DEC 26 1930

VOLUME 46 NUMBER 6

ARCHIVES

OF

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DECEMBER, 1930

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

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Archives of Internal Medicine

VOLUME 46 DECEMBER, 1930 NUMBER 6

THE DIFFERENTIATION AND SIGNIFICANCE OF CERTAIN OPHTHALMOSCOPIC PICTURES IN HYPERTENSIVE DISEASES *

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In the great attention that has been devoted in recent years to the hypertensive and renal diseases, ophthalmoscopic studies have not been neglected. Especially noteworthy in this regard are the investigations of Wagener and Keith and their co-workers [1] on the retinal changes in what they term malignant hypertension, of Moore [2] and O'Hare and Walker [3] on arteriosclerosis of the retina and of Volhard [4] on the pathogenesis of the retinal process. In the present communication, we shall report the results of studies on the correlation of the ophthalmoscopic observations with the individual renal and hypertensive diseases.

The material comprises studies of the patients with arterial hypertension and the nonhypertensive forms of "Bright's disease" admitted to Mount Sinai Hospital during 1928 and 1929. All cases were discarded in which the diagnosis did not seem clear clinically or was not checked at necropsy, as well as those instances in which adequate ophthalmoscopic studies were not made. There remained 274 cases, on which the figures given in this paper are based. Thirty-nine of the cases were also studied at necropsy. In addition, we have utilized a number of cases observed in Mount Sinai Hospital during other years, as well as some from Montefiore Hospital; these, however, have not been included in the statistics.

* Submitted for publication, May 19, 1930.
* From the Medical Services of Mount Sinai and Montefiore Hospitals.

1. Wagener, H. P.: Tr. Am. Ophth. Soc. **25**:349, 1927. Keith, Norman M.; Wagener, Henry P., and Kernohan, James W.: Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

2. Moore: Quart. J. Med. **10**:29, 1916; Medical Ophthalmology, ed. 2, London, J. & A. Churchill, 1925.

3. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis, Arch. Int. Med. **33**: 343 (March) 1924.

4. Volhard: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:422, 1921.

The subject matter will be considered under two general headings:

1. The three fundamental retinal lesions in hypertension.
2. The ophthalmoscopic observations in the individual hypertensive and renal diseases.

THE THREE FUNDAMENTAL RETINAL LESIONS IN HYPERTENSION

In the older literature, as well as in many recent publications, Liebreich's [5] term "albuminuric retinitis" is used as a generic designation for all the lesions of the retina, except for those due to closure of large vessels, that occur in patients with renal disease. However, in 1916, Moore [2] clearly differentiated the ophthalmoscopic picture produced by retinal arteriosclerosis from that which he termed "renal retinitis." More recently, he stated:

> I believe the general feeling of ophthalmic surgeons is that a fundus which shows numerous cotton wool patches, with edema and perhaps a retinal detachment, implies, not a different stage of disease, but a disease of a different type than that which is implied by a fundus showing marked vascular change, with numerous flame-shaped hemorrhages, little edema, a star figure composed of discrete dots, and no cotton wool patches. It will, however, be agreed that there are many intermediate cases which it is impossible to classify along these lines.

Moore does not attempt to correlate these different retinal lesions with individual types of renal disease. On the other hand, Keith, Wagener and Kernohan, on the basis of extensive investigations, believe that they can often differentiate the retinal lesions in the severe cases of essential hypertension which they term malignant hypertension from those which occur in glomerulonephritis. They found the following:

> In malignant hypertension the edema of the retina is less extensive and less dense, and there is little tendency to the formation of peripapillary snow-bank exudates. The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis. Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis.

As a result of the investigation of the material reported in this paper, we have come to the conclusion that the traditional unitary conception of "albuminuric retinitis" should be discarded; it is of great diagnostic and prognostic importance to differentiate three ophthalmoscopic pictures that may appear in patients suffering with diseases characterized by arterial hypertension: 1. Retinal arteriosclerosis and arteriosclerotic retinopathy. 2. Malignant hypertensive neuroretinitis. 3. Choked disk due to increased intracranial pressure.

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5. Liebreich: Arch. f. Ophth. **5**:265, 1859.

RETINAL ARTERIOSCLEROSIS AND ARTERIOSCLEROTIC RETINOPATHY

In this group the changes in the fundus are the result of retinal arteriosclerosis. The retinal arteries show the characteristics of more or less marked arteriosclerosis, namely, irregularity of lumen, so-called arteriovenous compression, irregular light reflex, copper-colored appearance, white lines accompanying the blood columns ("perivasculitis"), etc. Generally, some constriction of the arteries, particularly of the smaller branches, can be made out, but this is, as a rule, not nearly as marked as in malignant hypertensive neuroretinitis. Increased tortuosity and a brilliant light reflex are often also considered as signs of arteriosclerosis, but their significance is difficult to evaluate. It should be pointed out that "arteriovenous compression," which is generally not actual compression but displacement of the vein by the artery passing over it into deeper portions of the retina, is not necessarily a sign of retinal arteriosclerosis but may be present in marked form merely as a manifestation of hypertension. This is proved by the fact that it is sometimes observed in cases of acute glomerulonephritis and hypertensive toxemia of pregnancy before there is time for the development of sclerosis. Possibly, the mechanism in such cases is that the artery with high blood pressure is more rigid than the normal vessel, much as a rubber tube becomes more rigid if fluid is forced through it under high pressure. In other cases, however, the venous compression is a direct consequence of the arteriosclerosis, for Friedenwald [5a] found "actual encroachment of the thickened arterial and venous walls upon the common space within the common arteriovenous fibrous coat at the point of crossing." Evidences of retinal phlebosclerosis may also be present, and the veins may be distended, particularly if there is cardiac insufficiency.

The disk shows no abnormalities in most instances; in others, there is slight haziness of the outlines. In far advanced cases, there may be atrophic changes. The absence of papilledema is the most important criterion for differentiation from malignant hypertensive neuroretinitis.

The retina may not be demonstrably altered despite marked arteriosclerosis, or the changes may be extensive. Hemorrhages are often present. They may be single or multiple, large or small, superficial or deep, with or without relation to the larger vessels. White spots ("exudates") [6] may be absent or present either in small numbers or

5a. Friedenwald: The Pathology of the Eye, New York, The Macmillan Company, 1929, p. 170.

6. The almost universal use of the word "exudate" as a general term for white and yellowish areas in the fundus in hypertensive diseases is unfortunate. Such areas are most often not manifestations of exudation, but result from degenerative or proliferative processes.

profusely. Most often, the individual opacities are of small size; when such small spots are numerous, they give the "powdery" appearance. In other cases, they are large. When large, they often appear shiny, and their outlines are sharply delimited from the adjacent retina ("hard"), thus differentiating them from the "cotton-wool" patches found in malignant hypertensive neuroretinitis. The lesions may be white, yellowish or ivory-colored. Rather exceptionally, the spots may form a stellate figure around the macula or may have an irregular circinate arrangement in this region. Evidences of choroidal sclerosis with pigment changes are often present.

While retinal arteriosclerosis, as far as we have observed, is always bilateral, though often of greatly different intensity in the two eyes, the changes in the retina are not uncommonly unilateral for a long time. The picture may change strikingly from time to time. This is most often due to hemorrhages appearing or clearing up. But the white spots may also come and go; in a recent case they disappeared completely on two occasions.

As mentioned, this retinal picture is to be regarded as due to arteriosclerosis of the retinal arteries. When well marked, it is found only where hypertension has existed for a considerable time,[7] and almost always other evidences of marked arteriosclerosis can be found in the larger vessels of one region or another (extremities, aorta, coronaries, cerebral arteries, etc.). The large majority of cases in which the picture occurs are those of essential hypertension. But we have also seen a considerable number of examples in glomerulonephritis of many years' duration. We have also observed the typical picture in a patient with hypertension due to amyloid contracted kidney. Particularly exquisite examples of the arteriosclerotic fundus are to be found in patients suffering from both diabetes and essential hypertension; the condition in these cases constitutes the so-called diabetic retinitis. According to

7. In accordance with the observations of O'Hare and Walker,[3] we have found that marked retinal arteriosclerosis is practically pathognomonic of hypertension, either manifest or preexistent. In those cases in which we have noted marked retinal arteriosclerosis in the presence of normal blood pressure, there was cardiac enlargement or other evidence that hypertension had previously existed; as a rule, the disappearance of the hypertension was due to coronary artery disease. In a series of fifteen old patients who had marked arteriosclerosis of the radial and other large accessible arteries ("senile" arteriosclerosis) without any evidences that hypertension had ever been present, signs of retinal arteriosclerosis were either absent or but slight. The most frequent change in the retinal arteries of these patients was moderate thinning of the blood columns. The opportunity of examining some of these arteriosclerotic patients without evidence of hypertension, past or present, was given to us by Dr. Frederick D. Zeman and Dr. Robert K. Lambert.

the description given by Duckworth,[8] gouty retinitis (with which we have no personal experience) is apparently of this type, for he described hemorrhages as the outstanding feature in the presence of "small" arteries and the absence of optic neuritis.

The significance of arteriosclerotic retinopathy, severe though the changes in the retina may be, is purely that of arteriosclerosis. It does not necessarily indicate, as does malignant hypertensive neuroretinitis, that renal insufficiency either is present or threatens almost inevitably. The large majority of our patients with arteriosclerotic retinopathy who have died—they may live for many years with these retinal changes—have not succumbed to renal insufficiency but to cardiac failure, coronary closures, cerebral vascular disease, etc. When renal insufficiency does appear in patients with arteriosclerotic fundi, it tends to be less rapidly progressive than in those with malignant hypertensive neuroretinitis.

MALIGNANT HYPERTENSIVE NEURORETINITIS

This variety of retinal change is of much more ominous prognostic significance than the arteriosclerotic retinal lesions just described. It is characterized by the presence, generally though not invariably from the onset, of papilledema in addition to the retinal lesions. In view of this fact and the serious prognostic significance, it may be termed malignant hypertensive neuroretinitis.

As a rule, the appearance of papilledema is the first change in the fundus (apart from the usually antecedent constriction of the arteries), though most cases are first observed when retinal lesions are also present. In several instances that we have seen, the presence, alone or predominantly, of papilledema led to the suspicion of tumor of the brain. In most of our cases, the elevation of the disk was not notable, but Keith, Wagener and Kernohan, and Larsson[9] described an elevation of as much as 6 diopters. As a rule, the presence of peripapillary edema and the consequent absence of abrupt transition make estimation of the elevation difficult or impossible. (Larsson carried out his measurements with the Gullstrand ophthalmoscope, which we have not used.) In most instances of essential hypertension with papilledema, the disk is reddened, but if there is also marked anemia, which occurs most often in glomerulonephritis, but also in the terminal uremia of essential hypertension, the disk may be very pale. In unusual cases of long standing, atrophy of the nerve finally supervenes.

8. Duckworth: A Treatise on Gout, Philadelphia, P. Blakiston's Son & Company, 1889, p. 94.

9. Larsson, S. W.: Acta ophth. **1**:193, 1924.

In some instances, well marked changes (exudate and hemorrhages) may appear in the retina before the papilledema. These cases are rather exceptional, and the papilledema is generally not long in making its appearance.

In the retina, hemorrhages are generally, though not always, present; they are of various sizes and shapes and may be either deep or superficial. White spots are usually also present. Contrary to those found in the arteriosclerotic retina, these opacities are most often of the soft, indistinctly bordered type often described as "cotton-wool." They may be very large and numerous and may merge so as to form an extensive peripapillary ring or cover practically the entire central retina. "Hard," sharply delimited opacities, the type seen in the arteriosclerotic retina, are often also present and in prolonged cases tend largely to replace the cotton-wool areas. A stellate figure may be formed about the macula.

The arterial blood columns are narrowed, generally to a striking and sometimes to an extreme degree. The degree of narrowing of different vessels varies in many instances. The narrowing of the arterial blood columns is, as far as we have observed, the first change in the ophthalmoscopic picture that later develops the features just described. However, marked narrowing of the retinal arteries may exist in hypertensive patients for long periods, as we have repeatedly observed, without the appearance of changes in the disk or the retina. There can be no doubt that the narrowing of the arterial blood columns is the result of functional vasoconstriction of the musculature of the retinal arteries, for it may appear early in the course of acute glomerulonephritis or the hypertensive toxemia of pregnancy before there is any opportunity for narrowing of the lumen by a proliferative process.

Arteriosclerosis of the retinal arteries may or may not accompany this form of retinal lesion. In long-standing cases of essential hypertension or chronic glomerulonephritis, evidences of arteriosclerosis are generally present and may be marked. On the other hand, if the retinal lesions occur in hypertension of relatively recent inception, as in the toxemia of pregnancy, the early stages of glomerulonephritis, or often in the malignant forms of essential hypertension in young persons, retinal arteriosclerosis is absent. The veins are generally distended, particularly when there is marked papilledema.

Malignant hypertensive neuroretinitis occurs in glomerulonephritis and essential hypertension; details of this occurrence and its significance are given in the following sections. It is present frequently in the hypertensive toxemia of pregnancy with or without eclampsia gravidarum. It also may appear in lead poisoning with hypertension; this

may occur in the absence of renal involvement (Oliver,[10] De Schweinitz[11]). Finally, we[12] have observed it in a case of hypertension due to suprarenal tumor in which the kidneys were healthy.

PATHOGENESIS

In the efforts to clear up the pathogenesis of "albuminuric retinitis," attempts have been made to correlate the retinal lesions with five different manifestations of Bright's disease:

1. Renal insufficiency.
2. Retinal arteriosclerosis.
3. Increased intracranial pressure.
4. Hypercholesterolemia.
5. Arterial hypertension.

Renal Insufficiency.—Most of the early investigators believed the retinal lesions to be a consequence of renal insufficiency, the resulting abnormalities in the composition of the blood causing the retinal changes. Later, Widal, Morax and Weill[13] attributed the retinal changes to retained products of protein metabolism, for they found nitrogen retention in each of seventeen patients with retinal changes. However, this theory is entirely untenable, for retinal lesions of even extreme severity may occur in the presence of intact renal function; as Keith and his co-workers have emphasized, this occurs especially in essential hypertension, but we have also seen it in glomerulonephritis. In fact, malignant hypertensive neuroretinitis may occur in the presence of anatomically intact kidneys, as we observed in a case of hypertension resulting from suprarenal tumor. Because of the great theoretical importance for the pathogenesis of neuroretinitis in hypertensive disease of this case, which we[12] have reported in detail from another point of view, the salient features will be mentioned here.

Case 1.—A man, aged 24, was admitted to Mount Sinai Hospital on Jan. 11, 1923. He had suffered from dyspnea on exertion and palpitation for three months. There were also precordial pain and a dry cough.

The patient breathed rapidly and with obvious effort. His heart was enlarged to the left and the right; a presystolic gallop rhythm was heard. The radial artery felt thickened; the blood pressure was 200 systolic and 150 diastolic. Pulsus alternans was present. There was no evidence of impairment of renal function; the specific gravity of the urine reached 1.025, and six days before death, the

10. Oliver, in Allbutt's System of Medicine, New York, The Macmillan Company, 1898, vol. 2, p. 973.

11. de Schweinitz: Toxic Amblyopias, Philadelphia, Lea Brothers & Company, 1896, p. 126.

12. Oppenheimer, B. S., and Fishberg, A. M.: Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

13. Widal, Morax and Weill: Ann. d'ocul. **143**:354, 1910.

urea nitrogen content of the blood was 11.9 mg. per hundred cubic centimeters. Albuminaria was generally, though not always, present while casts were seen only occasionally.

The ophthalmoscopic observations were as follows: In the right eye the nerve head was red; its margins were indistinct. The veins were engorged, the arteries extremely narrow and in places lost. There was perivasculitis. The left eye was the same as the right eye, but there were numerous fine spots of degeneration between the nerve head and the macula and a few larger white areas near the nerve head.

The symptomatology in the hospital was that of progressive myocardial insufficiency. The patient was subsequently transferred to Montefiore Hospital, where he developed bronchopneumonia; he died on March 27.

At necropsy the heart was found to be enormously hypertrophied and dilated (weight, 880 Gm.), the left ventricle being most affected. There were only slight changes in the kidneys. There was a hypernephroma of the right suprarenal gland and multiple adenomas of the left suprarenal gland. Further details of the clinical and anatomic observations will be found in our previous paper.

A similar case has since been reported by Winkel.[14]

On the other hand, renal insufficiency in glomerulonephritis, urinary obstruction and other conditions may be present for a long time and terminate in fatal uremia without retinal lesions. For these reasons, it seems clear that renal insufficiency in itself does not cause the retinal lesions.

Retinal Arteriosclerosis.—Von Michel[15] and other earlier investigators considered "albuminuric retinitis" to be due to retinal arteriosclerosis. It is true that retinal arteriosclerosis does cause lesions of the retina, but this type, as we have seen, is to be differentiated from the type of retinal change considered in this section. In these cases, which we term malignant hypertensive neuroretinitis, retinal arteriosclerosis and its consequences may be present if there has been hypertension for a long time; in instances in which the hypertension is of brief duration, arteriosclerosis is absent. Anatomic demonstrations of this fact have been given by Schieck[16] and others. That arteriosclerosis cannot be incriminated in the pathogenesis of the retinal process in acute glomerulonephritis or the toxemia of pregnancy is obvious.

It will be pointed out that in all cases of malignant hypertensive retinitis in essential hypertension that we were able to study at necropsy, necrosis of the renal arterioles was present. Whether a similar necrotizing process occurs in the retinal arterioles and contributes to the retinal mischief, we are unable to say. In a few sections of eyes in our cases that we have seen through the courtesy of Dr. I. Goldstein and Dr. D.

14. Winkel, M.: Deutsches Arch. f. klin. Med. **159**:1, 1928.

15. von Michel: Ztschr. f. Augenh. **2**:1, 1899.

16. Schieck: Ber. ü. d. Versamml. d. 34 deutsch. ophth. Gesellsch. 1907, p. 77.

Wexler, necrosis of the retinal or choroidal arterioles was not present. The question is being studied by Dr. Goldstein and Dr. Wexler, who will report their results.

Endarteritic lesions of the retinal and choroidal arteries, characterized by endothelial proliferation, are often, though not always, present in malignant hypertensive neuroretinitis. But they are too inconstant to be regarded as the primary cause of the lesions, and it is possible that they are secondary to the retinal process.

Increased Intracranial Pressure.—Cushing and Bordley [17] described a remarkable case of chronic renal disease with severe retinal lesions in which the intracranial tension was so enormously increased that subtemporal decompression was carried out. Larsson [9] found increased intrathecal pressure in each of eleven patients with hypertensive neuroretinitis, and expressed the belief that it may play a rôle in the pathogenesis of the lesion. However, increase in the cerebrospinal tension is present in only some of the patients with hypertensive neuroretinitis; in others, despite marked swelling of the disk and severe retinal lesions, as we have repeatedly observed, the intracranial tension is within normal limits and cannot be concerned in the pathogenesis of the retinal changes. However, there are instances of hypertensive disease in which edema of the brain does produce enormous increase in intracranial pressure and consequent choked disk; such cases form a class apart and will be considered in the subsequent material.

Hypercholesterolemia.—Because cholesterol esters are present in large quantities in many of the white lesions of the retina and because of the occurrence of hypercholesterolemia in some varieties of renal disease, Chauffard [18] advanced the hypothesis that hypercholesterolemia is the cause of the retinal lesions. However, this hypothesis is not of general validity, for in the large majority of instances of essential hypertension or chronic glomerulonephritis of many years' standing with retinal lesions, hypercholesterolemia is absent. In chronic nephrosis in which hypercholesterolemia is generally marked, the retinal changes do not occur. It is possible, however, that when retinal lesions occur in subacute or early chronic glomerulonephritis, the presence of hypercholesterolemia may result in increased deposition of cholesterol in the retinal plaques.

Arterial Hypertension.—It was pointed out by Traube,[19] in 1861, that retinal lesions occur only in those forms of renal disease in which there is hypertrophy of the left ventricle. All subsequent observations

17. Cushing and Bordley: Am. J. M. Sc. **136**:484, 1908.

18. Chauffard; Font-Reaul and Laroche: Compt. rend. Soc. de biol. **73**:283, 1912.

19. Traube: Gesammelte Beiträge **2**:985, 1870.

have borne out this observation. We have never seen an instance of so-called albuminuric retinitis in which there was not evidence of hypertension, past or present. Rarely, one encounters a patient with typical retinal changes in whom the blood pressure at the time of observation is not elevated. The instances of this variety that we have seen have been of two kinds: 1. The blood pressure has fallen in the terminal stages of uremia or as a result of disease of the coronary arteries. 2. In rare instances in children the retinal changes may occur with a relatively moderate hypertension, which is, in fact, proved to be hypertension only by the subsequent course of the case. Thus, in one such case in a child of 10 years, the blood pressure was only 124 systolic and 86 diastolic, but after recovery it was 95 systolic and 55 diastolic.

Not only is hypertension present in every instance of "albuminuric retinitis," but invariably, as far as we are aware, it precedes the appearance of the retinal lesions. As yet unsolved, however, is the problem of the nature of the connection between arterial hypertension and the retinal process. Why is hypertension present in a maximal degree in many cases without affecting the retina, while in other cases it induces only arteriosclerotic changes in the retina, and in still others the malignant hypertensive neuroretinitis here under discussion? Volhard [4] advanced the theory that the retinal lesions are manifestations of ischemia of the retina produced by a spasm of the retinal arteries which is part of the widespread vasoconstriction that is present in arterial hypertension. Among the evidence in favor of this theory are the following facts:

It was pointed out long ago by Gowers [20] that in hypertension the arterial blood columns in the retina are often narrowed. This is particularly marked, in fact often extreme, when malignant hypertensive neuroretinitis is present.

A number of observers (Elschnig,[21] Wagenmann,[22] Labadie-Lagrave and Laubry [23] and others) have observed spasms of the retinal arteries in hypertensive states. Recently, Haselhorst and Mylius [24] not only observed but photographed cramplike and rapidly changing contractions of the retinal arteries in a patient with eclampsia gravidarum. After two days the contractions became more constant and involved longer stretches of the arteries. At this time the first white degenerative lesions in the retina appeared.

20. Gowers: Brit. M. J. **2**:743, 1876.
21. Elschnig: Wien. med. Wchnschr. **48**:1305, 1898.
22. Wagenmann: Arch. f. Ophth. **43**:219, 1897.
23. Labadie-Lagrave and Laubry: Tribuna méd. **38**:437, 1906.
24. Haselhorst, G., and Mylius, K.: Zentralbl. f. Gynäk. **52**:1180, 1928.

Ophthalmoscopic pictures similar to that of "albuminuric retinitis," even including the stellate figure about the macula, have been observed in the anemia of chlorosis, with improvement after disappearance of the anemia (de Schweinitz,[25] Augstein[26]).

As a result of the circulatory disturbance in the retina produced by increased intracranial tension (e. g., in tumors of the brain with choked disk), changes may appear in the retina indistinguishable from those of malignant hypertensive neuroretinitis.

In view of these facts, it would seem that Volhard's theory that "albuminuric retinitis" is due to ischemia of the retina resulting from spastic contraction of the retinal arteries is deserving of serious consideration, although it cannot by any means be considered as established.

CHOKED DISK DUE TO EDEMA OF THE BRAIN

In hypertensive states, as a result of circulatory disturbances in the brain correlated with the hypertension (Oppenheimer and Fishberg[27]), edema of the brain may develop, with a resultant increase in intracranial pressure. The manifestations of increased intracranial pressure—headache, nausea, vomiting, convulsions, choked disk, high pressure of the cerebrospinal fluid, etc.—may so dominate the clinical picture that a diagnosis of tumor of the brain is made, as has occurred several times in our experience.

Cases of choked disk due to edema of the brain in hypertensive states have been described by Cushing and Bordley,[17] Volhard,[4] Blackfan and Hamilton[28] and others. We have seen several such cases. They occur in glomerulonephritis, the hypertensive toxemia of pregnancy (eclampsia gravidarum) and, judging by the literature, lead encephalopathy. We have not encountered this syndrome in essential hypertension. As previously mentioned, the choked disk may be accompanied by changes in the retina appearing identical with those of malignant hypertensive neuroretinitis.

OPHTHALMOSCOPIC OBSERVATIONS IN THE INDIVIDUAL HYPERTENSIVE AND RENAL DISEASES

THE FUNDUS IN GLOMERULONEPHRITIS

The cases of glomerulonephritis are considered in two groups, one including the acute and subacute cases, and the other chronic glomerulo-

25. de Schweinitz: Diseases of the Eye, ed. 10, Philadelphia, W. B. Saunders Company, 1910, p. 499.

26. Augstein: Klin. Monatsbl. f. Augenh. **63**:174, 1919.

27. Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive Encephalopathy, Arch. Int. Med. **41**:264 (Feb.) 1928.

28. Blackfan, K. D., and Hamilton, B.: Boston M. & S. J. **193**:617, 1925.

nephritis. Any dividing line between the two groups is of necessity purely arbitrary. We have included in the class of acute and subacute glomerulonephritis the cases of five months' or less duration when the patient is first admitted to the hospital. This time was chosen, because when glomerulonephritis has lasted half a year or more, the chances of complete recovery are rather small, and the term "chronic glomerulonephritis" conveys the notion of little likelihood of restitutio ad integrum.

ACUTE AND SUBACUTE GLOMERULONEPHRITIS

There were twenty-seven cases of this variety, in twenty-one of which arterial hypertension was demonstrated during the stay in the hospital. Of the twenty-seven cases, severe ophthalmoscopic changes were present in only two. In one of these the picture was typical of malignant hypertensive neuroretinitis, and the patient, a boy aged 14, died within two months of the appearance of the retinal lesions. The other patient was a child, aged 10, with glomerulonephritis, who developed papilledema with an elevation of 1.5 diopters and flame-shaped hemorrhages in the retina; the process was evidently of the nature of a beginning choked disk due to increased intracranial pressure, for it was accompanied by the Babinski sign and other evidences of cerebral implication. In eight other cases of acute and subacute glomerulonephritis, there were slight ophthalmoscopic abnormalities, either haziness of the papilla or constriction of the arteries, or both. In one instance there was considerable diffuse edema of the retina.

These observations are in accord with the general experience that severe changes in the fundus occur in only a small proportion of cases of recent glomerulonephritis. The small incidence of severe retinal lesions in acute glomerulonephritis is probably correlated with the fact that hypertension, the pathogenic factor underlying the retinal lesions, is marked and persistent in only a small part of the cases, though present at one time or another in the large majority of instances. Slight changes, notably narrowing of the arteries or haziness of the disk, are found in a considerable proportion of the cases, particularly if the fundus is examined repeatedly. They have no especial prognostic significance. The same is true of the occasional small hemorrhages that are found in the fundi; they may be present in the absence of notable hypertension and are apparently akin to the purpuric spots in the skin that are not uncommon in acute glomerulonephritis.

It is important from prognostic and therapeutic points of view that the ophthalmoscopic picture of malignant hypertensive retinitis be differentiated from the choked disk that results from edema of the brain. The presence of the latter conveys no implication as to the likelihood of

the appearance of renal insufficiency, and if the patient can be tided over the acute cerebral episode, complete recovery often follows. On the other hand, the appearance of true malignant hypertensive neuroretinitis in acute glomerulonephritis is of ominous prognostic significance; most such cases go on to renal insufficiency and uremia, though occasionally improvement and even recovery occur.

CHRONIC GLOMERULONEPHRITIS

Fifty-five cases of glomerulonephritis of more than five months' duration were studied. The large majority of the cases were of a duration of a number of years; in most of these long-standing cases it was impossible to determine even approximately the time of onset.

The direct correlation between arterial hypertension and retinal lesions in these fifty-five instances of chronic glomerulonephritis is immediately obvious from table 1.

TABLE 1.—*Chronic Glomerulonephritis*

	Number Cases	Number Cases with Diastolic Pressure Over 100 Mm.	Number Deaths While in Hospital
Negative fundus	24	7	5
Retinal arteriosclerosis	8	8	0
Arteriosclerotic retinopathy	6	6	3
Malignant hypertensive retinopathy	17	15*	11

* The two patients with malignant hypertensive retinitis in whom the diastolic blood pressure was under 100 mm. were admitted to the hospital shortly before death; in both instances, left ventricular hypertrophy was found at necropsy, demonstrating that hypertension had existed.

The fundus in chronic glomerulonephritis will be treated under the following headings:

Normal Fundus.—In twenty-four of the patients with chronic glomerulonephritis significant changes in the fundus were not observed. In this group are included several instances in which narrowing of the arteries or haziness of the margins of the disks was noted, but which progressed no further during the period of observation. As table 1 shows, most of the patients with negative fundi had no hypertension while in the hospital, but in seven this was present, having been, in fact, as high as 210 systolic and 150 diastolic in one instance. In most of the patients with hypertension but negative fundi there was reason to believe that hypertension had not been present for a long time. It is true that in one of the patients who died at the age of 30 the renal disease had started twelve years previously, but we had no means of learning what the blood pressure had been during these years.

In the cases of chronic glomerulonephritis of the so-called nephrotic type, i. e., those cases in which the clinical picture is dominated by intense albuminuria and edema in the absence of more than slight hypertension, the fundus exhibits no change. In a high proportion of cases of chronic glomerulonephritis in children hypertension is long absent and so are retinal lesions. The same is true of subacute bacterial endocarditis which is often complicated, particularly in the bacteria-free stage, by glomerulonephritis. Finally, when chronic glomerulonephritis occurs in a tuberculous person, it is rarely marked by either hypertension or retinal lesions; in one such case in the foregoing series, the glomerulonephritis was present for years and was finally terminated by death from uremia, but neither hypertension nor retinal lesions ever developed.

Five of the patients suffering from chronic glomerulonephritis who had normal fundi died. Four of the deaths were from uremia, illustrating the long known fact that glomerulonephritis can progress to renal insufficiency and fatal uremia without the development of retinal lesions. However, such cases are much outnumbered by those with retinal lesions (table 1).

Retinal Arteriosclerosis and Arteriosclerotic Retinopathy.—In eight of the cases of chronic glomerulonephritis retinal arteriosclerosis was the only ophthalmoscopic observation, and in six others, the retinal arteriosclerosis was accompanied by the retinal changes which we described as arteriosclerotic retinopathy. Retinal arteriosclerosis and its consequences were also present in some of the patients who had malignant hypertensive retinitis, but these instances are considered with the latter change. In all instances of glomerulonephritis with retinal arteriosclerosis, the renal disease had been present for some years, in several for many years. Moore mentioned a case in which retinal arteriosclerosis developed within a few months; no such instances were included in our cases. All of the patients with retinal arteriosclerosis had diastolic blood pressures of over 100 mm. (table 1). The ophthalmoscopic pictures were the same as those seen when retinal arteriosclerosis or arteriosclerotic retinopathy occurs in essential hypertension. In the cases that came to necropsy, the glomerulonephritis was accompanied by arteriolosclerosis and usually by marked general arteriosclerosis; as is the case in essential hypertension, the retinal arteriosclerosis is but one manifestation of the injury to the arteries, and particularly of the arterioles, wrought by long-standing hypertension. The following case illustrates arteriosclerotic retinopathy occurring in chronic glomerulonephritis.

Case 2.—A man, aged 38, was admitted to the hospital in a state of uremic coma. He had been ill with anasarca and suppression of urine at the age of 7

years. Little was known of his intervening history except that he had suffered from headaches for twelve weeks. The blood pressure was 158 systolic and 102 diastolic.

Ophthalmoscopic examination revealed both nerve heads to be clear in outline though somewhat pale (hemoglobin, 45 per cent). The arteries were markedly constricted and revealed the typical evidences of extreme arteriosclerosis described in the foregoing paragraphs. In both eyes there were recent small round hemorrhages near the disk, as well as round atrophic areas representing absorbing and absorbed hemorrhages.

The patient died a week after admission, and at necropsy chronic glomerulonephritis with marked secondary contraction was found; the process was obviously of many years' standing.

Malignant Hypertensive Neuroretinitis.—This retinal picture was found in seventeen of the patients. All of these patients gave evidence of either present or past hypertension (table 1). In most, the hypertension was marked, averaging decidedly higher than in the other groups. Fifteen of the seventeen patients had renal insufficiency with nitrogen retention. Of the remaining two, one had good renal function, while the kidneys of the other were shown to be functionally impaired by the defective outcome of the concentration test though the blood chemistry was still normal (compensated stage of impaired renal function). Eleven of the seventeen patients died while in the hospital, and several of the others were discharged in a condition in which it was evident that they would not long survive. All of the deaths were due to uremia. The long known unfavorable prognosis in this variety of retinal change is thus substantiated in the present series.

THE FUNDUS IN ESSENTIAL HYPERTENSION

In this category we have included those of our patients with arterial hypertension in whom the elevation of blood pressure was not associated with glomerulonephritis or mechanical obstruction of the urinary passages. There were 189 such cases. The ophthalmoscopic observations and certain other data are summarized in table 2.

Normal Fundus.—In thirteen of the patients with essential hypertension, ophthalmoscopic examination revealed no abnormalities. In several of these cases the hypertension was not severe and in three it was intermittent, evidently being in the initial phase of the disease. In none of these cases was renal function demonstrably impaired. Only one of the patients with normal fundi died; in this instance, cerebral hemorrhage was the cause of death, and the kidneys also revealed but slight arteriolosclerosis at necropsy.

Contracted Arteries.—Marked narrowing of the arterial blood columns was observed in eleven of the patients. It should be mentioned

that contraction of the retinal arteries was present in all of the patients with malignant hypertensive neuroretinitis and in many of these with arteriosclerotic fundi, but here we include only those cases in which narrowing of the arterial blood columns was the sole abnormal feature. Of these patients, two had impairment of renal function, in both instances of the compensated variety with normal blood chemistry. None of the patients died while in the hospital.

Retinal Arteriosclerosis and Arteriosclerotic Retinopathy.—Retinal arteriosclerosis in the absence of changes in the retina or nerve head was observed in 70 of the patients. In 58 other patients the retinal arteriosclerosis had produced changes in the retina; in many of the cases choroidal lesions were also observed. Furthermore, in 32 of the 37 patients with malignant hypertensive neuroretinitis, retinal arterio-

TABLE 2.—*Essential Hypertension*

Ophthalmoscopic Observations	Number Cases	Deaths in Hospital	Renal Function		
				Impaired	
			Unimpaired	Compensated	Decompensated
Normal fundus	13	1	13	0	0
Contracted arteries	11	0	9	2	0
Retinal arteriosclerosis	70	9	57	11	2
Arteriosclerotic retinopathy	58	5	37	12	9
Malignant hypertensive retinitis	37	13	11	7	19

sclerosis was also present. Thus, 160, or 84 per cent, of our 189 patients with essential hypertension had retinal arteriosclerosis.

Prognostically, the presence of retinal arteriosclerosis or arteriosclerotic retinopathy is of significance in that it indicates that the hypertension has probably been present for a considerable time. In accord with this, it is seen from table 2 that the mortality and incidence of impairment of renal function in the patients with retinal arteriosclerosis is much higher than in those without retinal changes. On the other hand, they are much lower than in those with malignant hypertensive neuroretinitis. Moreover, as will be discussed, the rate of impairment of renal function in these patients is much slower than that in those with neuroretinitis. Patients with essential hypertension and retinal arteriosclerosis or arteriosclerotic retinopathy may get on well for many years. However, most of the patients with severe arteriosclerotic retinopathy have evidences of arteriosclerotic disease in other organs, most often the heart or the brain, and their outlook is rather poor. An exception is, however, often constituted by patients with both diabetes mellitus and essential hypertension; such patients may have marked arteriosclerotic

retinopathy ("diabetic retinitis") with hemorrhages and areas of retinal degeneration for years while leading tolerably useful lives.

Malignant Hypertensive Neuroretinitis.—This condition was present in thirty-seven of our patients. The long known serious prognostic implication of this type of retinal lesion is immediately obvious from table 2; thirteen of the patients died of uremia while in the hospital and several more were removed in a precarious condition. In twenty-six of the patients, renal function was impaired. In nineteen of the twenty-six the impairment of renal function had reached the decompensated stage as shown by the retention of nitrogen in the blood. In accordance with the observations of Keith and his co-workers, malignant hypertensive neuroretinitis may appear in a patient with essential hypertension while renal function is not demonstrably impaired, and this adequate functional state of the kidney may persist for a considerable time, exceptionally even for years. However, more often such patients soon show evidence of functional impairment of the kidneys. The progress of the impairment of renal function in the presence of malignant hypertensive neuroretinitis is generally much more rapid than in patients with only arteriosclerotic changes in the fundus.

The reason for the rapid progress of impairment of renal function in most cases of essential hypertension with malignant hypertensive neuroretinitis seems clear from the anatomic observations in those of our cases that came to necropsy. In all ten of the necropsies in cases in which the patients had had essential hypertension and malignant hypertensive neuroretinitis, necrosis of the arterioles in the kidney was found.[29] In all instances the anatomic picture of the kidneys was that described by Fahr [30] as "malignant sclerosis," namely, necrosis, endarteritis and thrombosis of the renal arterioles, necroses and proliferative changes in the glomeruli, in addition to the arteriolosclerosis and glomerular hyalinization which are also found in the usual ("benign") case of essential hypertension. On the other hand, necrosis of the renal arterioles was not present in any of the eleven cases of essential hypertension without malignant hypertensive neuroretinitis in which the patients came to necropsy.

As far as our material is concerned, then, the presence of malignant hypertensive neuroretinitis in essential hypertension is diagnostic of the occurrence of necrosis of the renal arterioles. We suspect, however, that the retinal changes may precede the actual appearance of arteriolar necrosis in the kidneys, for the following reasons: In several of the

29. The anatomic studies were made by Dr. Paul Klemperer.

30. Fahr, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, p. 405.

cases, the retinal changes had been present for many months before death. From the appearance of the necrotic lesions in the renal arterioles, however, one is led to the belief, although not the certainty, that they are of relatively recent inception. Moreover, in some of the cases the retinal lesions appeared while renal function was good and the urine exhibited only a faint trace of albumin and no blood. It scarcely seems probable that widespread necrosis of the renal arterioles with its inevitable consequences in the glomeruli should be present for any considerable time without manifesting itself in urinary changes. In several cases which later showed necrosis of the renal arterioles, we believed that we had detected the onset of arteriolar necrosis in the kidneys by the appearance of blood and larger quantities of albumin in the urine. Conceivably, then, a patient with essential hypertension and malignant hypertensive neuro-

TABLE 3.—*Age Incidence of Retinal Lesions in Essential Hypertension*

Age, Years	Normal Fundus	Narrow Arteries	Retinal Arterio-sclerosis	Arterio-sclerotic Retinopathy	Malignant Hypertensive Neuro-retinitis
0- 9	0	0	0	0	1
10-19	0	0	0	0	1
20-29	1	0	1	0	2
30-39	4	1	7	7	12
40-49	6	7	18	15	14
50-59	1	2	22	26	7
60-69	1	1	18	9	0
70-79	0	0	4	1	0

retinitis may sometimes succumb before necrosis of the renal arterioles has occurred, but we have not yet observed such a case.

Malignant hypertensive neuroretinitis and the renal arteriolar necrosis it portends may appear at any stage of essential hypertension. In some of our cases, the patients had been known to suffer from essential hypertension for many years—in one instance more than twenty years—before a turn for the worse occurred and the neuroretinitis was discovered. However, in contradistinction to the arteriosclerotic retinal changes, neuroretinitis affects a decidedly higher proportion of the younger patients with essential hypertension than the older. This is shown in table 3.

The higher incidence of malignant hypertensive neuroretinitis in the younger age groups of patients with essential hypertension corresponds to the well known fact that the clinical course in such persons tends to be much more severe and rapidly fatal than in older persons with high blood pressure. The anatomic basis for this severe course lies in the fact, pointed out in the foregoing paragraphs, that those patients with essential hypertension who have neuroretinitis develop necrosis of the

renal arterioles. The necrosis of the renal arterioles with its attendant changes in the renal parenchyma results in severe and generally rapidly progressive renal insufficiency.

Parenthetically it may be remarked that while the presence of malignant hypertensive neuroretinitis in a patient with essential hypertension indicates that necrosis of the renal arterioles is either present or will appear, it does not have this significance in glomerulonephritis. In fact, we had not observed arteriolar necrosis in chronic glomerulonephritis—although it does occur in the acute and subacute stages of the disease—until Dr. Paul Klemperer recently showed us this change in such a case. Even in this instance, only isolated arterioles were affected.

THE FUNDUS IN AMYLOID KIDNEY

In the vast majority of instances of amyloid disease of the kidneys, there are no retinal changes. The reason is, of course, that arterial hypertension is rare in amyloid kidney. However, there are cases of renal amyloidosis with hypertension, and in extremely rare instances this results in retinal lesions. Dickinson [31] mentioned such a case, and Litten [32] observed two instances of typical "Bright'sche Retinitis" in several hundred cases of amyloid disease. In their recent paper on amyloid contracted kidney, Noble and Major [33] mentioned in a table that albuminuric retinitis was present in one case. In our series, there was a case of amyloid contracted kidney with arteriosclerotic retinopathy. As such cases are apparently great rarities, the principal features will be summarized briefly.

CASE 3.—M. C., a man, aged 37, was admitted to Mount Sinai Hospital on Nov. 14, 1929, complaining of pain in the left side of the chest and left shoulder and vomiting.

Since the age of 5 years he had suffered from tuberculosis of the left hip, a sinus persisting despite three operations. He had had nocturia (up to six times a night) as far back as he could remember. For three years previous to admission to the hospital he had suffered from headaches; sometimes these were accompanied by nausea and vomiting, which had become much more frequent. About six weeks before admission he began to suffer from pain in the left shoulder and precordial region which radiated down the left arm to the finger tips. At first this pain appeared only after walking or other exercise, but shortly before admission it also manifested itself when he was at rest, especially at night.

At the time of admission to the hospital the patient was emaciated. There was a diffuse brownish pigmentation of the skin, probably largely the result of treat-

31. Dickinson: Treatise on Albuminuria, ed. 2, New York, William Wood & Company, 1881, p. 190.

32. Litten, in Zuelzer and Oberlaender: Klinische Handbuch der Harn- und Geschlechtsorgane, Leipzig, F. C. W. Vogel, 1894, vol. 2, p. 131.

33. Noble, J. F., and Major, S. G.: Renal Insufficiency in Amyloid Disease, Arch. Path. **8**:762 (Nov.) 1929.

ment with ultraviolet rays. In the region of the hip was a draining sinus. The heart was slightly enlarged to the left. The liver and spleen were not demonstrably enlarged. The blood pressure was as high as 196 systolic and 116 diastolic. The urine contained a small quantity of albumin and a few casts. Study of renal function revealed it to be severely impaired; in a concentration test the specific gravity did not rise above 1.012, and the blood contained 70 mg. of urea nitrogen per hundred cubic centimeters. The Bennhold test with congo red showed that only 22 per cent of the dye remained in the blood stream at the end of an hour, instead of the normal of over 70 per cent; in the absence of great albuminuria, such a result is highly suggestive of the presence of amyloidosis.

Opthalmoscopic examination revealed the presence of arteriosclerotic retinopathy. The retinal arteries showed a moderate degree of arteriosclerosis. The disks appeared normal. Above, below and to the temporal side of the right disk were linear hemorrhages, in close relation to the vessels. About half way between the left disk and the macular region was a white area of degeneration, roughly triangular and sharply delimited. There were several minute white areas above the macula. In the right retina were two small hemorrhages.

The condition of the patient rapidly became worse, and retention of urinary constituents in the blood became more severe (urea nitrogen, 224 mg. per hundred cubic centimeters). He died of uremia on December 19.

At necropsy amyloid contracted kidneys obviously of long standing were found.

SUMMARY

1. In 274 cases of hypertensive and renal diseases the ophthalmoscopic observations have been studied in relation to the clinical picture; in 39 of the cases, postmortem observations were also made.

2. The concept of albuminuric retinitis includes three distinct pathogenetic entities, which can most often be differentiated with the ophthalmoscope: (*a*) arteriosclerotic retinopathy, (*b*) malignant hypertensive neuroretinitis and (*c*) choked disk due to increased intracranial tension from edema of the brain.

3. The ophthalmoscopic characteristics of these three types of retinal changes are described, and their occurrence and prognostic significance in the individual types of hypertensive disease investigated.

4. In all of the ten cases of essential hypertension with malignant hypertensive neuroretinitis in which the patients came to necropsy, necrosis of the renal arterioles was present. On the other hand, necrosis of the renal arterioles was absent in eleven instances of essential hypertension without malignant hypertensive neurotinitis that were studied at necropsy.

5. Instances are described of malignant hypertensive neuroretinitis in a patient with arterial hypertension due to suprarenal tumor and of arteriosclerotic retinopathy accompanying hypertension resulting from amyloid contracted kidney.

DOES CLIMATE AFFECT THE HUMAN CONCEPTION RATE?*

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In an effort to ascertain the extent of climatic effects on the human organism in health and disease, we have studied its effect on such metabolic diseases as diabetes mellitus, pernicious anemia, exophthalmic goiter and Addison's disease. In these diseases there was found a distinctly lowered death rate in the warmer regions that show, in general, a depression of the metabolic rate by the heat. The people of these regions possess relatively low blood pressures, and have distinctly less angina pectoris than is found in the cooler countries.

Since the climatic effects mentioned are probably exerted mainly through the endocrine glands (pancreas, thyroid, suprarenals), it was deemed advisable to determine whether a similar depression was exercised on the sex glands. For this purpose the birth statistics of different cities, states and countries were obtained. The numbers of births in each month for a number of years were taken, the mean for each month obtained, and the twelve months equalized to a thirty-one day basis for comparison. Due attention was paid to February irregularities in this calculation. Also, where the population of the unit studied changed more than 1 per cent a year during the period covered by the statistics used, due correction was made for the effect of this increase or decrease on the monthly birth rate during the mean year. The corrected monthly births were then transposed to conception times by counting back nine months and ten days, and these "conceptions resulting in live births" were plotted as shown in the graphs. It is, of course, obvious that any climatic effect should be expected to be correlated directly with conception time rather than with the time of birth, since births are only more or less inevitable consequences of the conceptions.

For a number of localities the mean temperature, relative humidity and rainfall by months are also charted to show their relationship to the monthly conception curve. All graphs are drawn with the bottom of the chart as the zero line.

Beginning with the more northern cities and countries, we see the conception rate in Montreal to be rather depressed in the late winter,

* Submitted for publication, May 21, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

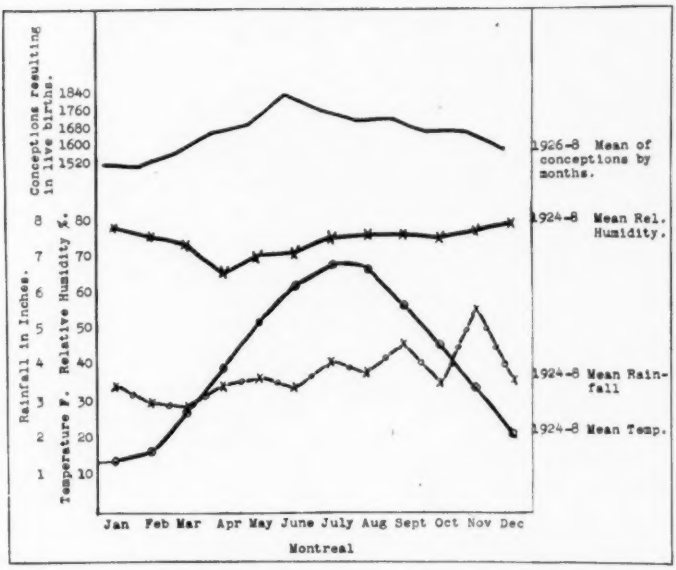

Chart 1.—Seasonal variations in the conception rate in Montreal.

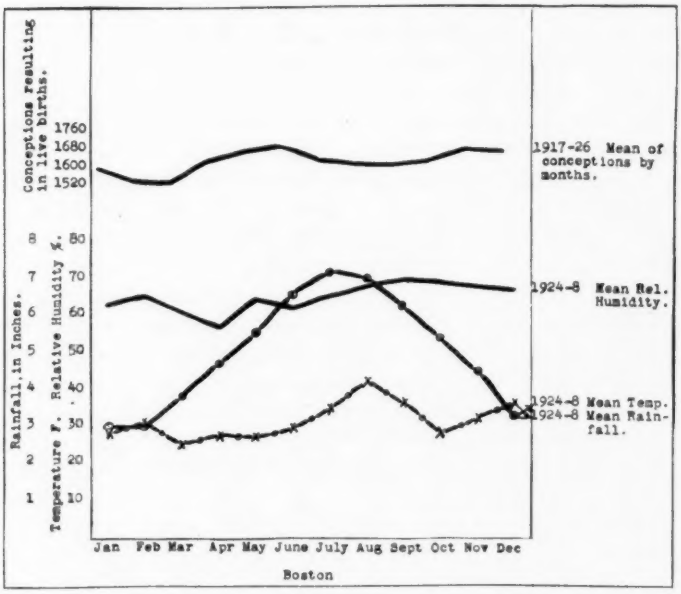

Chart 2.—Seasonal variations in the conception rate in Boston.

to rise steadily to a June peak, and then to decline gradually again to late winter. The rise in the mean monthly temperature to about 68 F. for July and August seems to be without depressive effect on conceptions.

A little farther south, however, where the mean monthly temperature for July and August rises above 70 F., there is a depressive influence on conceptions. Boston, with a July and August mean of 71 F., shows a 6 per cent reduction in conception rate. Chicago exhibits a marked late winter depression and a mild summer heat effect.

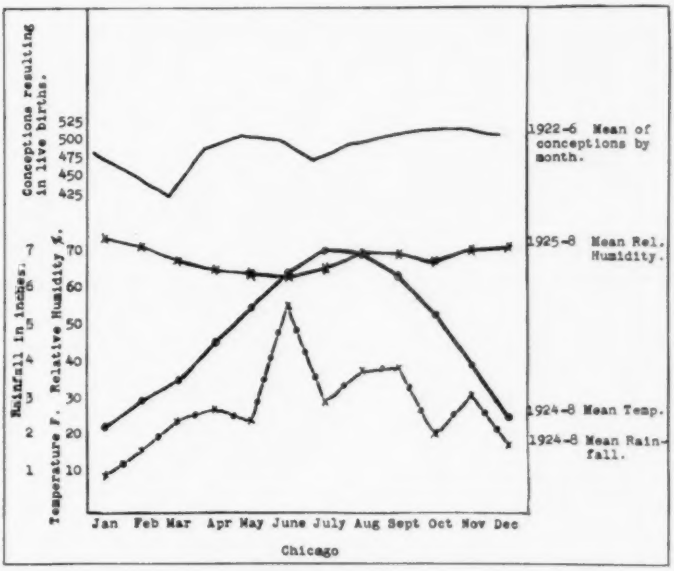

Chart 3.—Seasonal variations in the conception rate in Chicago.

Wichita, Kan., in which the mean July and August temperature rises to 78 F., suffers a 14 per cent reduction in the conception rate. The mean temperatures of 82 F. in Charleston, S. C., and 83 F. in Tampa, Fla., are accompanied by corresponding depressions of 27 and 31 per cent in the conception rate.

On the other hand, in the cities of the Pacific Coast, where the mean temperature is more stable, in no case rising above 70 F. for the summer months, there is no summer depression of conceptions. Even as far south as San Diego and Los Angeles, there is no significant summer effect.

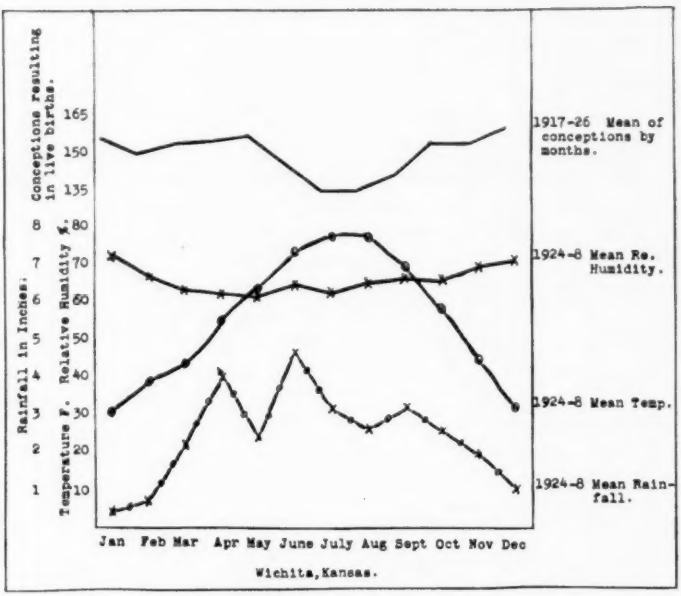
Conceptions resulting in live births.
Rainfall in Inches.
Temperature F. Relative Humidity %.
1917-26 Mean of conceptions by months.
1924-8 Mean Re. Humidity.
1924-8 Mean Temp.
1924-8 Mean Rainfall.
Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec
Wichita, Kansas.

Chart 4.—Seasonal variations in the conception rate in Wichita, Kan.

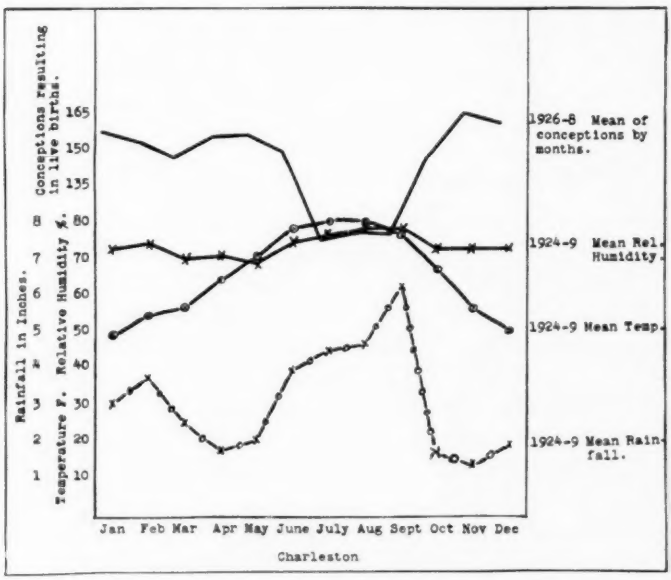
Conceptions resulting in live births.
Rainfall in Inches.
Temperature F. Relative Humidity %.
1926-8 Mean of conceptions by months.
1924-9 Mean Rel. Humidity.
1924-9 Mean Temp.
1924-9 Mean Rainfall.
Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec
Charleston

Chart 5.—Seasonal variations in the conception rate in Charleston.

A similar study of states in various latitudes from Maine to Florida gives results similar to that from the cities. In the north the spring depression is most marked, with the rate highest in the summer; in the central states the heat depression of July and August is evident, and farther south this becomes more and more marked.

In order to show that the variations in conception rate are not necessarily correlated with the marriage rate, graphs are shown for Belgium and Switzerland. Here it is seen that although the June peak in con-

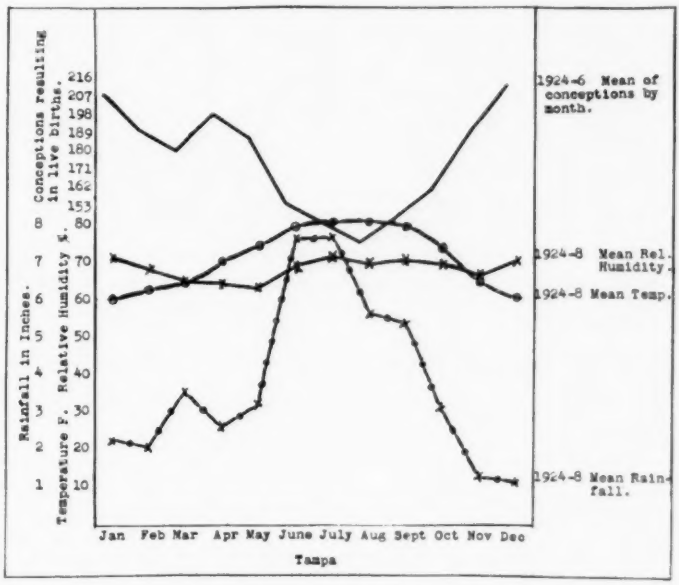
Rainfall in Inches.
Temperature F. Relative Humidity %.
Conceptions resulting in live births.
1924-6 Mean of conceptions by month.
1924-8 Mean Rel. Humidity.
1924-8 Mean Temp.
1924-8 Mean Rainfall.
Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec
Tampa

Chart 6.—Seasonal variations in the conception rate in Tampa,Fla.

ceptions coincides well with a similar marriage peak, the fall marriage peak does not produce a noticeable effect on conceptions.

In Japan the climatic effects are most striking. The spring months of April, May and early June are almost perfect so far as temperature is concerned, but from the middle of June to early September the humidity is almost constantly high, day and night, while the mean temperature rises to 99 F. The mean monthly temperature and rainfall recorded on the graph represent the means obtained for 1928 from nine observation stations scattered throughout Japan. The graph shows the striking changes produced in the conception rate by these climatic changes. There is a 50 per cent fall in conceptions during their tropical

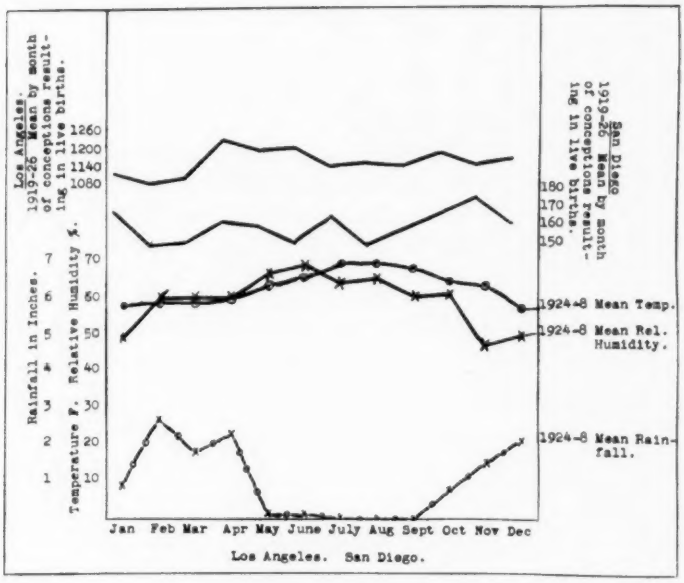

Chart 7.—Seasonal variations in the conception rate in Los Angeles and San Diego.

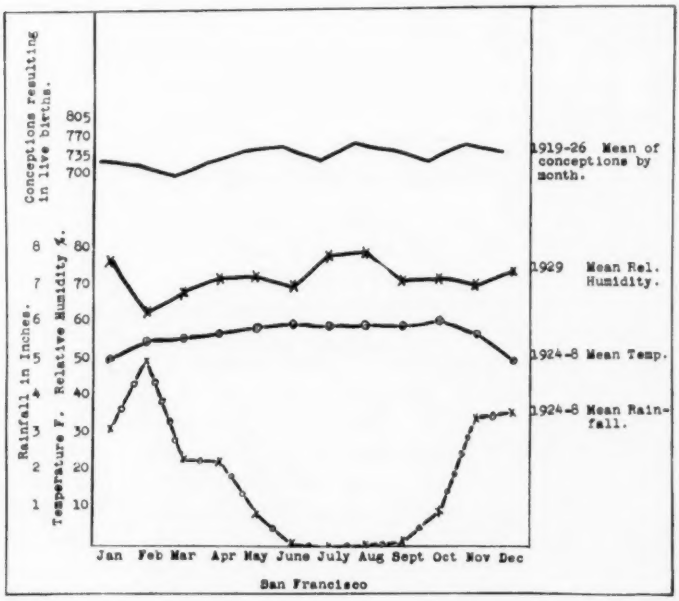

Chart 8.—Seasonal variations in the conception rate in San Francisco.

summer period! Calculation has shown that not over 10 per cent of the spring rise in conceptions here could be attributed to the increase in the marriage rate.

No doubt many persons reading this article will be inclined to attribute the depressions in conception rate during the hot months to a diminution in the frequency of intercourse during the hot weather, but such

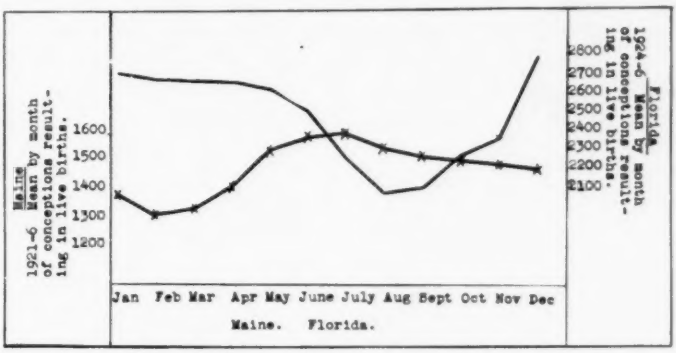

Chart 9.—Seasonal variations in the conception rate in Maine and Florida.

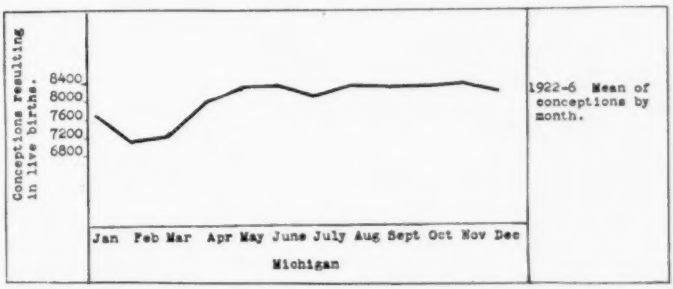

Chart 10.—Seasonal variations in the conception rate in Michigan.

is not the case. Dr. T. J. LeBlanc (personal communication) obtained statistics on the frequency of use of houses of prostitution by the male population of Japan, and these statistics show no significant depression of male sexual activity during the hot summer months. We may, then, conclude that male sexual activity is not much influenced by heat, and in a country like Japan it is mainly the male that dominates this question. Since Japan shows the most marked seasonal variations in conceptions, the inference is that a biologic reduction in fertility is produced by the heat.

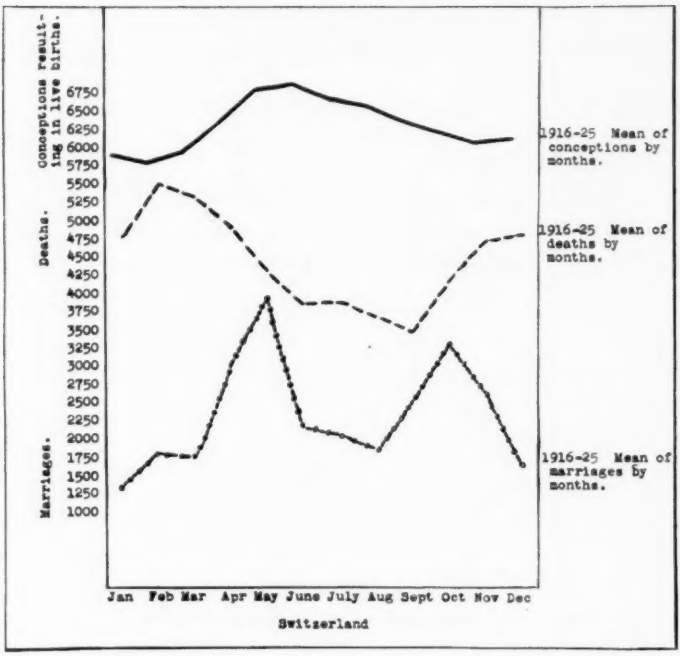

Chart 11.—Seasonal variations in the conception rate in Switzerland.

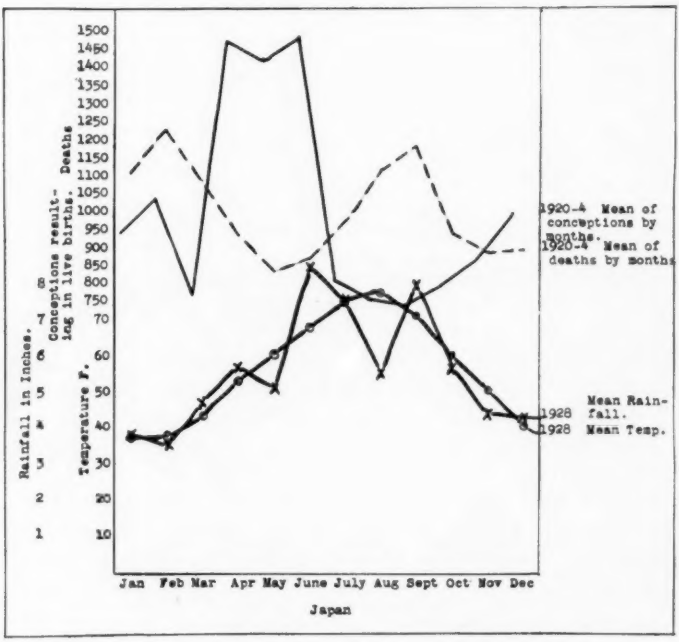

Chart 12.—Seasonal variations in the conception rate in Japan.

It cannot be demonstrated at present whether only one sex or both are involved in the depression. It is known that raising the temperature of the testicles by 2 or 3 C. (35.6 or 37.4 F.) will inhibit spermatogenesis. Some stock breeders claim that a ram loses his effectiveness in the summer if his scrotum is enclosed in heavy flannel to retain body heat.

While there seems to be no doubt, from the graphs presented, that there is a seasonal depression in conceptions when the mean monthly temperature rises above 70 F., it must not be inferred that the annual birth rate in the tropics is lower than that in the temperate regions. Indeed, just the opposite is the case; but too many factors enter into determining the total birth rate for us to derive any value in discussing it here. Different populations should not be compared in this respect; but we may well compare seasonal changes occurring in given populations.

In 1925, Reed [1] presented graphs of the monthly birth rate in the United States and Great Britain. From the graphs presented in the present article it is seen that there is really no single seasonal birth curve in this country, the north and south being almost the reverse of each other. It is of special note to observe that the peak of conception rate in the various graphs presented most often occurs when the mean monthly temperature is around 65 F. It was at about this same temperature that Huntington [2] found human efficiency along various lines of endeavor to be highest.

In conclusion, we may state that human fertility, as indicated by the conception rate, is highest in any given population at a temperature of about 65 F., and that it is reduced during the low temperatures of the northern winter and by mean summer temperatures above 70 F. The summer depression is roughly proportional to the rise in the mean temperature above 70 F. These changes in conception rate are not dependent on changes in the marriage rate or sexual activity of the population, and must therefore represent actual variations in human fertility.

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1. Reed, Lowell J.: Am. J. Pub. Health **15**:948, 1925.

2. Huntington, Ellsworth: World Power and Evolution, New Haven, Conn., Yale University Press, 1920.

VITAL CAPACITY IN COLLEGE WOMEN

I. STANDARDS FOR NORMAL VITAL CAPACITY IN COLLEGE WOMEN *

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A former paper [1] on vital capacity in college women included standards derived from the physical examinations of 1,150 Wellesley freshmen. The apparatus was as good as was available when the data were gathered, 1922 to 1924, and it was used with systematic regard for accuracy. To verify or revise these standards, the vital capacities of the freshmen at Mount Holyoke College were carefully taken during the years 1925 to 1929 by the department of physical education, with an excellent Collins spirometer. The group, after the omission of oriental students and those with crippled thorax, numbered 1,337, and was, as far as is known, a typical group of freshmen—healthy young women aged about 18. The age range was small, from 16 to 23, with the very great majority from 17 to 19 years of age.

Since it became apparent from the observation of many students that those who were most likely to give inaccurate results in the regular fall physical examination were the students with low vital capacity, all students in this group were reexamined, and about one-third raised their records appreciably. They either had not understood how to use the spirometer the first time, simple as the test is, or embarrassment prevented their showing what they really could do. Their second figures were approximately like those that they repeat throughout their course. This merely indicates the need of careful and repeated studies of students in working with any functional test, if the results are to be valid. Speed in giving the tests cannot be paramount, as it too often is in the rapid routine of the freshman examination.

The statistical treatment of the figures was made by the usual methods. Our results were verified by the department of statistics of the Harvard School of Public Health, and regression equations were derived by them for the prediction of vital capacity from height, weight and surface area. They also prepared the charts for easier comparison of individual cases with normal results.

The results of this study are given in the table. Figures from the Wellesley group and also those from the Stanford study of Pasmore

* Submitted for publication, June 25, 1930.

* From the Department of Physiology, Mount Holyoke College.

1. Turner, A. H.: The Vital Capacity of College Women, Am. Phys. Ed. Rev. **32**:593, 1927.

and Weymouth [2] are given for comparison with the recent figures from the Mount Holyoke group. The data in the Minnesota study by Boynton [3] are unfortunately not in a form for ready comparison, nor are the tables for women compiled by Myers,[4] but a footnote to the table indicates the general nature of these results. The methods used in obtaining data at McGill University (Herriott [5]) are not fully enough

Determinations on Five Freshmen Classes at Mount Holyoke College, 1925 to 1929 Inclusive, Totaling 1,337 Students *

	Mount Holyoke	Wellesley	Stanford
Number tested	1,337	1,150	430
Averages:			
Height, cm.	162.83	162.9	161.5
Weight, Kg.	55.50	54.97	54.9
Surface area, sq.m.	1.58	1.585	1.571
Vital capacity,† liters	3.28	2.99	2.769
Standard deviations:			
Height	5.9065	5.685	5.37
Weight	7.1980	8.465	7.73
Surface area	0.1123	0.103	0.112
Vital capacity	0.4384	0.478	0.466
Coefficients of variation:			
Height	0.0360	0.0348	0.033
Weight	0.1297	0.154	0.122
Surface area	0.0711	0.065	0.071
Vital capacity	0.1329	0.159	0.169
Coefficients of correlation:			
Height : weight	0.4410	0.591	.....
Vital capacity : height	0.4958	0.354†	0.338
Vital capacity : weight	0.3754	0.2445‡	0.358
Vital capacity : surface area	0.4870	0.292§	0.400

* For comparison, figures from Wellesley and Stanford groups are also given. As compared with the tables of Myers, 1925, the figures from the Mount Holyoke group give about 107 per cent. Our averages were applied to his tables for calculating vital capacity from height and weight.

† Height and logarithm vital capacity were used here.

‡ Logarithm vital capacity and logarithm weight were used here.

§ Logarithm vital capacity and logarithm surface area were used here.

described to enable one to judge whether the spirometer used was comparable with that used at Mount Holyoke, but the figures are so far below those we obtained that they are not referred to in detail.

2. Pasmore, E. E., and Weymouth, F. W.: The Relation of Vital Capacity to Other Physical Measurements in Women, Am. Phys. Educ. Rev. **29**:166, 1924.

3. Boynton, R. E.: A Comparison of Normal Standards for the Vital Capacity of the Lungs of Women, Arch. Int. Med. **33**:292 (March) 1924.

4. Myers, J. A.: The Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925.

5. Herriott, J. S.: Research Quart. Am. Phys. Educ. A. **1**:46, 1930.

Points shown in the table to which attention is called are as follows: The vital capacity of the Mount Holyoke group is distinctly higher than that of the Wellesley group. Each year as the data were collected my associates and I saw this higher result, and in looking for a reason we seemed to find it in the ease with which the Collins spirometer is blown. In this instrument there is no constriction of the tube between mouth and bell, all moving parts are light, the bell is well counterpoised, and there is no excess pressure in the bell at the end. We think, therefore, that these results represent a real advance in accuracy, and not that the girls at Mount Holyoke are of higher vital capacity than are the Wellesley girls of approximately the same size. If vital capacities are to mean anything in the study of human welfare, they must be taken with care to secure the subject's real maximum. The improvement also in the correlation of these measurements with other bodily measurements may indicate that these figures are better ones. It is of interest to note that the average vital capacity in liters divided by the average surface area gives 2.07, practically West's figure of 2 liters per square meter of body surface as the normal for women,[6] and when the vital capacity in cubic centimeters is divided by the average height in centimeters one obtains 20.1, again almost the same as West's formula for women of 20 cc. for each centimeter of standing height.

The regression equations, which were determined for the several correlations, are given here. This is a more accurate mode of prediction than the simple device just mentioned. By them, the average vital capacity for any height, weight or surface area can be calculated easily. For instance, let x equal the measured height; then y, the average vital capacity, can be obtained by substituting for x the observed height in the equation. Surface area is derived from height and weight according to the method of DuBois,[7] for which nomogram and tables are readily found.

Height	$y = 0.0368x - 2.706$
Weight	$y = 2.017 + 0.023x$
Surface area	$y = 0.279 + 1.901x$

By looking at the coefficients of correlation, it will be noted that the equations for height and surface area give much better modes of prediction than that for weight.

From charts 1, 2 and 3, the average vital capacity for any observed height or weight or calculated surface area can be quickly determined.

6. West, H. F.: Clinical Studies on the Respiration, Arch. Int. Med. **25**:306 (March) 1920.

7. DuBois, D., and DuBois, E. F.: Clinical Colorimetry, Arch. Int. Med. **17**:863 (June) 1916.

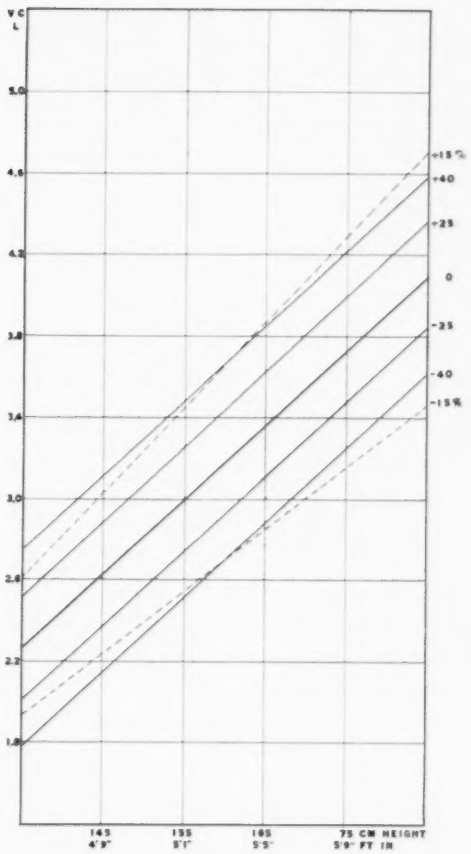

Chart 1.—The average vital capacity for young adult women of any height and the position of 50 and 80 per cent of the groups of different heights. In this and the following charts, *v.c.* indicates vital capacity; the 0 line, the line of average vital capacity for the heights given at the bottom of the chart; the + 25 and — 25 lines, the limits of 50 per cent of the vital capacties; the + 40 and — 40 lines, the limits of 80 per cent of the vital capacities. Above line + 15 per cent and below line — 15 per cent lie the vital capacities that are removed by more than 15 per cent from the average value. To find average vital capacity: from height of subject at bottom of chart proceed vertically to line "0"; at the left margin opposite this intersection will be found the average vital capacity for the height in question.

Find the observed or calculated measurement at the bottom of the chart. Follow the proper line vertically until it intersects the oblique line 0; then proceed from this intersection to the left margin where the average vital capacity for the measurement in question will be found in liters. With this the subject's actual vital capacity can be readily compared.

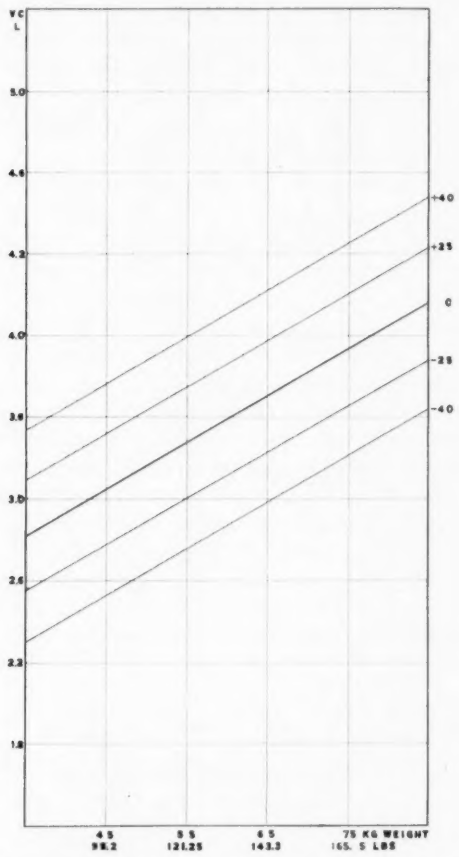

Chart 2.—The average vital capacity for young adult women of any weight and the position of 50 and 80 per cent of the groups of different weights.

Vital capacity varies much among persons of a single height, weight or surface area. It is desirable, therefore, not only to know that a particular subject is, say, 10 per cent low in vital capacity, but to know how many other persons of that height show the same figure. On the charts, the lines + 25 and — 25 include between them 50 per cent of

the whole number of persons measured; the lines + 40 and — 40 similarly include 80 per cent of the total number. We should expect to find, then, about 10 per cent of any large group above the + 40 line and as many below the — 40 line.

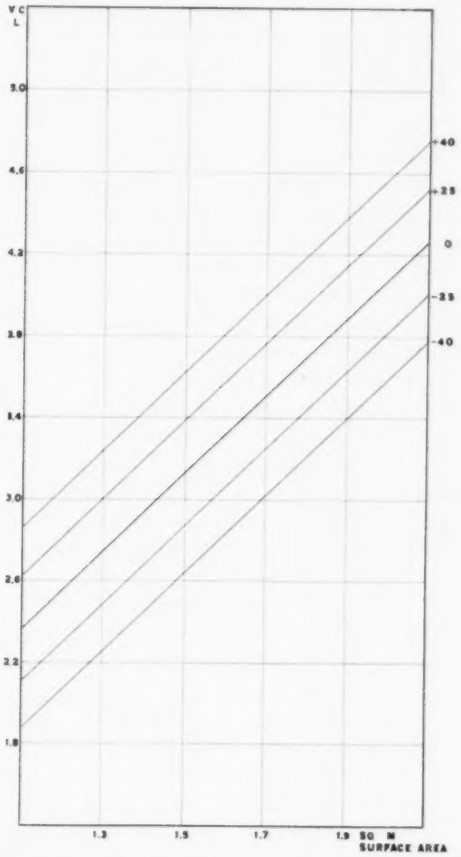

Chart 3.—The average vital capacity for young adult women of any surface area and the position of 50 and 80 per cent of the groups of different surface areas. Surface area is derived from height and weight according to the DuBois method.

It has been possible to try out the usefulness of these determinations on one class at Vassar College through the cooperation of Dr. Charlotte Haywood of the Physiology Department who charted last fall's freshman class of 285 students. The averages for this class are height,

165.6 cm.; vital capacity, 3.396 liters. By reference to our height chart, it is seen that for the height 165.6 cm. the average vital capacity is 3.39, as close an agreement as could be asked. The distribution is as follows:

	Theoretical number	Observed
Above +40	28-29	34
Between +40 and +25	42-43	35
Between +25 and 0	71-72	65
Between 0 and −25	71-72	75
Between −25 and −40	42-43	54
Below −40	28-29	22

This agreement is approximately like that obtained from successive classes at Mount Holyoke. The high average height, vital capacity and high number above the +40 line in the Vassar study seem due to a considerable group of tall students with high vital capacity rather than to a general shift in the average, as is shown by the fact that of the total number more than half are below the 0 line. This skewness of distribution toward the high end of the vital capacity curve we also found at Mount Holyoke in nearly, though not quite, all classes studied. It may be related to the unequal participation of the students in sports, but this phase of the subject will be considered in the next paper.

In considering whether vital capacity is being measured as accurately as possible, McCloy [8] raised the question of the importance of temperature. Careful consideration has been given to the possibility of correcting to body temperature, as he suggests, the volume of air collected. There are serious difficulties in the way of making such a correction. Although the air in the machine cools rapidly to about the temperature of the room, if the machine is left filled, since the walls of the bell are thin and the metal so placed as to conduct heat easily to the water jacket, an accurate determination of the temperature of the expired air is not easy to obtain, because it probably changes at different rates in different cases, since some girls breathe out rapidly, some slowly. For the quantities of air concerned in our series, the variations on different days at the ordinary range of room temperatures, say 10 C. as a maximum, cannot be more than from 100 to 150 cc., a quantity within the range of variation in successive determinations made with all possible care by persons used to the machine. This room temperature quantity seems to fit the needs of the medical profession—to whom, after all, this measurement is of the greatest consequence—since simplicity of performance is much to be desired in any test. The differences, further, between the average vital capacity and any vital capacity that becomes important from the standpoint of disease or of physical fitness

8. McCloy, C. H.: Am. Phys. Educ. Rev. **32**:323, 1927.

will be of a much greater magnitude than the corrections involved for temperature. Hence, for reasons of general convenience and because the quantities involved are not greater than chance variations, it has seemed best not to attempt to introduce the temperature correction, tempting as it is from the standpoint of ideal accuracy.

SUMMARY

The study of the vital capacities of 1,337 freshman women at Mount Holyoke College has resulted in the presentation of a set of statistical data, regression equations and charts relating vital capacity to height, weight and surface area. The correlation with standing height is the best and with surface area only slightly less good. As previously determined, the weight correlation is distinctly less close.

VITAL CAPACITY IN COLLEGE WOMEN

II. A STUDY OF STUDENTS WITH HIGH AND LOW VITAL CAPACITY *

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Dreyer, the Englishman who has done so much work in vital capacity studies, is quoted by Myers [1] as follows: "If a person is found to have as much as 10 per cent less vital capacity than is normal for his class, it is *probable* that he is suffering from some health depressing condition, and if he is as much as 15 per cent below the normal limit, it is *practically certain* that he is abnormal in this respect." The work of Myers and others narrows the range of diseases expected to those of the lungs, heart and thorax.

It therefore seemed desirable to study carefully the students with low vital capacity in the group of 1,337 students used for the establishment of the new standards given in the first paper of this series (Turner [2]). All students more than 15 per cent under the average for their height (see chart 1, this issue, p. 933) have been kept under observation for a period varying from four academic years (two classes) to one academic year (the class entering college in the fall of 1929). This study was made with the cooperation of the medical department and the department of physical education. The program followed was that of interviews in the fall and spring with each student, at which times her vital capacity was checked and her athletic and health history talked over. A preliminary report on this study was made in 1927 (Turner [3]).

The following points were taken up, with the student, the college physicians, the gymnasium staff, or with all of them as became necessary:

1. Precollege history of activity as shown by participation in sports in and out of school, by summer programs, going to camps, and so on.

2. Special activities, such as prolonged study of vocal music or practice on wind instruments, etc.

3. Previous history of disease, especially those diseases affecting vital capacity (diseases of heart, lungs and thorax). One leading question that often brought evidence otherwise not recorded, in spite of medical histories given by parents

* Submitted for publication, June 25, 1930.

* From the Department of Physiology, Mount Holyoke College.

1. Myers, J. A.: The Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925.

2. Turner, A. H.: Vital Capacity in College Women. I. Standards for Normal Vital Capacity in College Women, this issue, p. 930.

3. Turner, A. H.: The Vital Capacity of College Women, Am. Phys. Ed. Rev. **32**:593, 1927.

and home physicians, was to ask if the student had ever been cautioned not to overdo physically, especially after an infectious disease.

4. History of dyspnea.

5. History during college years. Participation in sports at college and during the summers.

6. General health status in college and from physicians' records.

7. Change in vital capacity in college years. Special class in 1929-1930 for students with low vital capacity.

For purposes of comparison this group of 85 students with low vital capacity was checked continually with the students who were 15 per cent or more above the average for their height (see chart 1, this issue, p. 933). This group totaled 121, being more numerous because the distribution curve for vital capacities appears to be somewhat skew. This skewness may easily be related to athletic sports.

The first thing to be said regarding the results of the study is that all the students 15 per cent or more below the average do not show signs of present or past disease, contrary to the implication of the quotation from Dreyer with which this paper began. However, the second thing to be said is that there is a conspicuous difference between these students with low vital capacity and the average college group. The results are discussed briefly under the headings outlined. A table and notes will add further details.

RESULTS

1. *Precollege History of Activity.*—The students with high vital capacity were athletic; they joined in the sports of their preparatory schools, in the vigorous life of summer camps and in informal sports in their homes. The students with low vital capacity were in the main "quiet little girls"—there were few sports in either their school or summer histories. The reasons for this quiet life vary from real physical handicap, which was frequently found, to family influence, "My mother is afraid of the water," or to place of living, "I grew up in the Canal Zone; it's hot there!" or to lack of a school program.

Special mention should be made of swimming, which is by far the most conspicuous sport of students with a high vital capacity and of which many of those with low vital capacity know little or nothing. The former swim long distances, dive and swim under water; if the latter swim at all, they are hindered by being winded, or they swim very short distances. The importance of swimming was not recognized when this study was first begun, so the data for the first two classes are incomplete.

2. *Special Activities.*—Of the students with high vital capacity, four play on wind instruments, with years of practice behind them, two on the trumpet, one on the slide trombone and one on the clarinet; three

have had many vocal lessons; three have done significant work on farm or ranch; one is an Olympic swimmer. Two have lived in the country, where they "yelled" to see how far they could make their friends hear across country, a real sport for them. None of these factors are found in the group with low vital capacity.

3. *Previous History of Disease.*—In the group with low vital capacity there are each year a few students, perhaps three or four, with lasting cardiac defects either congenital or, more often, a sequel to some infection. These students are expected to have low vital capacity, but it is always surprising to find by no means all of the students with cardiac disorders in this group, for they are found in almost equal numbers in the normal group and even in the group with high vital capacity. Since it is difficult to find out the exact diagnosis in these cases, which obviously can be of little limitation or the students would not be in college, they have not been omitted from the group as a whole.

Myers [1] gives the average vital capacity for students who have had pneumonia as below the general average, but in the group of students with high vital capacity at Mount Holyoke there were proportionally almost as many persons who had had pneumonia as among the students with low vital capacity, and in the family history is noted seemingly equally severe disease. It seems, therefore, that in many cases the recovery is complete, and that one can have no assurance that an observed low vital capacity is due to pneumonia, though this may often be the case.

We have found no cases in which recovery from pulmonary tuberculosis has been known. There are several students in college with deformed thorax, in most cases due to infantile paralysis, but they were omitted from the study. In some of them the vital capacity gives little margin above the tidal air, and they suffer much from dyspnea. When the paralysis affected other muscles than those of the thorax, there was no indication of lowering of vital capacity, and such students were included.

4. *Dyspnea.*—The students in the group with low vital capacity are conscious of getting out of breath in ordinary life. Stairs are real obstacles, for they are often sadly out of breath on reaching the third floor office. Among them are some apparent exceptions, students who say they have no dyspnea, yet on further questioning say, "I never run." One student was kept out of the glee club because it was impossible for her to hold her breath long enough for the usual musical phrasing. Many suffer much in running, and in swimming they are held up for lack of "wind." A few seem not to suffer at all. Why do they not? They show persistently low vital capacity by all tests, yet they swim and they play at least moderately active games with no sense of limitation.

A careful study of this group would be of much interest, but there are few of them to study, not more than one or two a year.

Students in the group with high vital capacity suffer little from dyspnea except when participating in active sports like soccer and hockey or in fast swimming.

5. *College History: Sports.*—In the fall of the freshman year the first class teams show a marked preponderance of students with high vital capacity, though the basis of choice is success in playing the games. This preponderance continues throughout the college years. It is to be said, of course, that this group includes the long of limb and the broad-shouldered, students of past experience and success in the sports concerned, and one may be tempted to mix cause and effect. The students with low vital capacity are seldom found on class teams in the running sports, though a few appear in archery, volley ball and the like.

Many of the students high in vital capacity, but almost none of those low in vital capacity, are camp councillors during college years.

6. *College Health Status.*—One of the most interesting phases of this study was the rating of these two groups by the college physicians. Mount Holyoke is a residence college in a small town. The college medical department knows the medical history of each student rather fully, since contacts with outside physicians and specialists are made through the medical office. The physicians were asked to grade all members of these groups by this scale, A, excellent; B, good; C, fair; D, poor, a college health risk. The results surprised us by their clearness. The typical grade for the low vital capacity group is C, that for the high vital capacity group, A or B. In many cases the A's had never been mentioned in the college case histories.

In this connection the nutritional figures are of interest, though in the absence of standards that recognize varying widths of build as well as heights, we feel a lack of security in our results. They have not been tabulated, but there is no doubt of their general tenor. The girl with high vital capacity is not underweight—she is about what she should be for her build, or slightly overweight. The group with low vital capacity includes a large proportion of students who are markedly underweight and a few who are conspicuously overweight. The girls with high vital capacity are about 2.5 cm. taller than those with low vital capacity. The complete reasons for these differences are not known, but a future problem will be to consider the prevalence of healed rickets in the latter group. Their histories do not state whether they had rickets as babies or not; in fact, they do not know, but in several instances there is the high sternum to indicate thoracic involvement in babyhood. A further study is planned from this point of view.

7. Change in Vital Capacity During College Years.—For the entire group of 199 in the class of 1929 for whom determinations made during the freshman and senior years were available, the average increase was only 100 cc., scarcely any amount beyond the range of error. It thus appears that freshman standards may be considered suitable for adult young women. The students with high vital capacity change but little; practically none of them lose their high rating even though their activity may be very small after the college requirement in exercise is completed at the end of the sophomore year. Of a total of twenty-one students with low vital capacity who were followed through the four years, ten gained on the average 410 cc., an amount well above the general average for their classes. For these students there was no special program other than a general exhortation, when they came in for conference, on the benefits of sports. Four of this group lost an average of 260 cc. without known reason. The others showed no change.

Since it was apparent that at least some of this group with low vital capacity showed an increase, a special study was made of the group with low vital capacity of the fall of 1929, and twenty-five students were selected for special work in thoracic development and mobility under the direction of Miss Lillian Kuester, director of medical gymnastics at Mount Holyoke. Three of these students failed to report. The members of the group were given directions for suitable exercises, and were to report at intervals for conference and checking progress. The diligence of the group varied, but at the end of the year the results were these:

Total number	22
No change beyond ± 200 cc	11
Increase 210 to 400 cc	9
Average, 330 cc.	
Increase 410 cc. or more	2
Average, 600 cc.	

Of the eleven who did not gain, the reason for three may lie in pneumonia in the past and for one in a persistent cardiac limitation. Four reported only a few times and probably did not follow the program of exercise. There is no apparent reason for three, except that all had had little sturdy exercise in precollege days. The remark of one, "Mother was afraid of the water," is typical of the lack of appreciation of the value of sports in their homes. Of the eleven who showed good gains, two had had pneumonia, one had a persistent cardiac condition, and one was probably helped by an operation on her nasal septum which removed an obstacle to free breathing. But in the other cases we seemed to have the simple effect of a healthful reaction to wisely prescribed exercises. Several of these students reported a lessening of dyspnea, and, as they say, "more pep."

The training of students with low vital capacity in thoracic development and mobility will be continued in the next years until we have surer basis for judgment. At present, the indication is that many of our students with low vital capacity are so hampered, not because of any involvement by disease, but simply because they were cheated of their heritage through a life of too little sturdy exercise. The evidence points to the years of adolescence as the best time for such training, and the fact that many of our students with high vital capacity were for two years with little sturdy exercise in the last part of their college course shows that the power once gained is not readily lost. The question is not answered as to how far special training in college years, coupled with a gradually increasing participation in sports, may serve to raise vital capacity to a height associated with safety if not with athletic prowess. Thus far it appears that we have a good lead to follow in helping this group of physically deficient students to surer health.

There is no thought in this study that vital capacity has any magic relation to health, but merely that we have here one measurable function which is a part of the complex indicating an oxygen supply and delivery adequate for the needs of the body in strenuous exercise as well as in the quieter parts of the day's program. The material just described is summarized in more definite form in table 1.

Certain other matters are of interest, notably the comparative academic success in the two groups with which we are concerned. The average grades of the high and low vital capacity groups are given in table 2. Each successive class has shown this difference, which, though not very great, is undoubtedly of significance. The students at Mount Holyoke are given numbers which indicate their relative academic rank in their classes, the highest student in the class being ranked no. 1 and so on. The total number in a class is about 270. These average ranks of the high and low vital capacity group are included in table 2 and also the number of each group in the highest and lowest fifty students of the class. These records are based on as much of the students' work as was available during the spring of 1930, for one class four years, for a second three years, and so on. The present freshman class was not used at all. Whatever method is used, the result is the same, the students with high vital capacity are more successful academically though high vital capacity works no academic miracles.

There are several types of "honors," the giving of the degree with honor, honor scholars in the sophomore year, special prizes of various kinds. The greater success of the high vital capacity group is shown by this mode of judgment also.

TABLE 1.—*Comparison of Students Whose Vital Capacity Is More Than 15 Per Cent Above the Average for Their Height With the Group More Than 15 Per Cent Below the Average* *

	Vital Capacity More Than 15 per Cent High	Vital Capacity More Than 15 per Cent Low
Precollege sports †	Total 118	Total 84
Athletic	61.8%	10.7%
Nonathletic	38.2%	89.3%
Swimming ‡	Total 111	Total 72
Much	82.0%	39.0%
Not much	16.2%	40.2%
None	1.8%	20.8%
Previous diseases		
Pneumonia	15 students	12 students
Pleurisy	1	3
Heart limitation past or present	4	10
Rapid heart	1	2
Rheumatism	1	1
Tires easily §	1	9
History of dyspnea	Total 108	Total 84
Marked	7.4%	44.0%
In sports only	20.4%	33.4%
Not troubled	72.2%	22.6%
On college athletic teams #	90 instances	13 instances
College health rating ¶	Total 121	Total 84
A, excellent	38%	1.2%
B, good	53%	22.6%
C, fair	9%	72.5%
D, college risk	0	3.6%

* There are 121 students with high vital capacity and 85 with low vital capacity. Since the completeness of the records and the time in college varies, the total for each point studied is not always the entire number; however, when it differs from the whole number it is so stated. Since the number of students with high and low vital capacity is not the same, the results are frequently given in percentages rather than in actual numbers.

† "Athletic" indicates great participation in active school sports, nearly always membership on teams, frequent summers in camp, etc. "Nonathletic" means absence of the foregoing activities and slight activity in home or school life.

‡ The differences in the figures are obvious, but the real differences are still greater. The students who swim "much" in the high vital capacity group often swim a mile or more, dive, swim under water etc. Anything above 100 yards, if the swimming was frequent, was included in this group. Many of the students with low vital capacity can swim hardly more than this distance; "lack of wind" is often their limiting condition.

§ The parent or home physician often gives suggestive notes on the entrance blank. These comments are the ones meant here, not observation after college is reached.

Each student may be a member of a team in more than one year. She may also play on more than one team during the year, one in the fall, one in spring. Only the students who make the first class teams are included, not those on the substitute teams.

¶ Rating made by the college physicians.

TABLE 2.—*Academic Standing and Academic and Social Honors of Students with High and Low Vital Capacity* *

	High Vital Capacity	Low Vital Capacity
Academic average	81.19	79.39
Rank in class (highest student is no. 1), see text	114.5	138.0
Included in first 50 of the class	22	7
Included in lowest 50 of the class	12	16
Special academic honors (see text)	15	2†
Major offices (filled by student election)	15	2‡

* This study includes four classes, one for four years, one for three, and one for two, one for only one year. There were 87 students with high vital capacity and 56 with low vital capacity.

† One of the two students with low vital capacity having special academic honors is well-set up physically, though she is not athletic. Her vital capacity has increased by 400 cc. since she came to college two years ago, which takes her out of the low vital capacity class. She has a history of pneumonia in 1927, with probably a cardiac complication from which she may have been making a slow recovery. The other student is a typical student with low vital capacity in lack of exercise, poor color, poor posture and health record. Her vital capacity has not changed significantly in her three years of inactive college life.

‡ One of the two students having a major student office has none of the earmarks of low vital capacity. She plays games, she is the picture of health, she has a fine record academically and will doubtless take honors later on. Her vital capacity has increased by 360 cc. in her two years of college which takes her just above the 15 per cent low line. The other student is also successful in games and has a good health record, though she is no academic light. Her vital capacity is remaining about the same. Both these students evidently compensate in some way for the limitation they have in vital capacity.

There are each year about a dozen major senior offices to which students are elected by their fellow students. There are but few junior offices, and still fewer sophomore and freshman opportunities for this type of distinction. The number of such posts held by the high and low vital capacity groups is stated in table 2.

SUMMARY

A comparative study of students whose vital capacity was more than 15 per cent above or below the average for their heights was made to determine whether the group with low vital capacity showed signs of disease and whether, also, there were indications that vital capacity is an important function for judging physical fitness. These students were found in five freshman classes at Mount Holyoke College; there were 121 with high vital capacity and 85 with low vital capacity. Two classes were studied for four years, with two conferences each year for each student. The other classes were studied for shorter periods, as their year of entrance made possible.

While in a few instances there seemed to be direct association of low vital capacity with past or present disease of the thorax, heart or lungs, the majority of these students seemed to be young women for whom the exercise program in the years previous to college was very limited. The response of twenty-two students in one class, which has been specially trained for thoracic development, was gratifying. By whatever test this low vital capacity group was tried out, by the test of general health, of academic or of social success, it appears that it was truly at a disadvantage. There is thus the indication that vital capacity is a measurable function of significance in the general picture of the young women whose relative success in the field of health one is anxious to rate fairly. Two "morals" appear: one, the importance of sturdy exercise for girls, especially in their adolescent years, the other, the opportunity of bettering the low vital capacity and with it the general health of at least many of this group of students during their college years.

THYROTOXICOSIS FOLLOWING SUBTOTAL THYROIDECTOMY FOR EXOPHTHALMIC GOITER*

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Subtotal thyroidectomy for exophthalmic goiter is in general a remarkably successful operation. In most cases it is followed by a prompt and permanent drop in the basal metabolic rate to normal, and practically a complete disappearance of symptoms. However, in some instances the results are not so satisfactory. Either the thyrotoxicosis, although diminished, is not abolished, or else it disappears only to recur at a later date. The scarcity of accurate information in the literature with regard to the frequency, duration, types and causes of postoperative thyrotoxicosis led us to undertake the present study. It is an analysis of 190 unselected cases of exophthalmic goiter in which subtotal thyroidectomies were performed at the Massachusetts General Hospital during the six-year period from Jan. 1, 1923, to Dec. 31, 1928, and were followed by determinations of basal metabolism and clinical examinations for from three months to six years after operation.

THE FOLLOW-UP

The total number of patients who underwent subtotal thyroidectomy for exophthalmic goiter during the six-year period from 1923 to 1929 was 266. Of these, 76 were followed for less than three months after operation, and were therefore not included in this study. The remaining 190 were followed in the manner described.

Method.—With rare exceptions, a determination of basal metabolism (using the Benedict-Roth apparatus and the Aub-DuBois standards) was made each time the patient was seen in the clinic. Following this determination, the patient was examined in the laboratory, usually by us. No attempt was made to follow patients by letter.

* Submitted for publication, May 26, 1930.
* All of these data were collected in the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital. The expenses of preparation of the manuscript were borne in part by Rush Medical College.

Duration of Follow-Up.—In these 190 cases, the patients were followed for the following periods: three months to one year after operation in 75 cases, between one and two years in 36 cases, between two and three years in 33 cases, between three and four years in 20 cases, between four and five years in 19 cases, and between five and six years in 7 cases.

Frequency of Follow-Up.—The patients (37 in all) with postoperative thyrotoxicosis were followed thus: in 12 cases, once a month almost continuously for from four months to four and three-fourths years, including 3 cases followed for three, four and one-fourth and four and three-fourths years after operation; in 6 cases, once a month for from one and one-fourth to six and one-half years, with gaps of eight months to three and one-half years; in 14 cases, every two to three months with a few omissions for from five months to four and three-fourths years (this includes 5 cases followed two and one-half, 3, three and two-thirds, four and four and three-fourths years after operation); in 3 cases, every two to three months for from two to five years, with gaps of from one to one and one-half years, and in 2 cases, every three to six months for five and two-thirds and five and three-fourths years, with gaps of two and one-half and four and one-half years, respectively.

The 153 patients who were not thyrotoxic after operation were not followed so closely. However, about 55 were seen on an average of every one to three months; 10 of these for less than a year, and the other 45 for from one to four and one-half years after operation. The remaining 98 patients were seen at varying intervals, that is, every three or six months and then not again for a year or more, for as long as six years after operation.

TYPE OF OPERATION

The subtotal thyroidectomy was usually done in one stage, but in a few instances two hemithyroidectomies were performed a few months apart (15 patients in the postoperative nontoxic group and 7 patients in the postoperative toxic group).

According to the records, the subtotal thyroidectomies effected the removal of from two-thirds to nine-tenths of the thyroid gland. This, of course, does not give an accurate idea of the amount of tissue left in, as the glands varied so much in size. It was the practice of one of the surgeons doing the greatest number of thyroidectomies to leave in only from 1 to 4 Gm. of tissue on each side whenever possible, but he often unavoidably left more.

INCIDENCE OF THYROTOXICOSIS FOLLOWING SUBTOTAL THYROIDECTOMY

In some cases it was difficult to decide whether thyrotoxicosis was present. In many more patients than those included in the postoperative thyrotoxic group there was a slightly elevated basal metabolism at some time after operation (in general, plus or minus 15 per cent was taken as the normal range); but unless a high metabolism was persistent and was accompanied by definite clinical symptoms such as tachy-

cardia, undue nervousness, case of fatigue and excessive sweating, the patient was not considered thyrotoxic.

In the 190 cases that were followed, 153 (80.5 per cent) of the patients appeared to be cured, that is, they showed no definite thyrotoxicosis or no more than doubtful transient signs of it following operation. However, 37 (19.5 per cent) showed definite signs and symptoms.[1] The incidence of postoperative thyrotoxicosis by years is given in table 1. A possible cause for the high incidence in 1928 (31.1 per cent) will be discussed later.

SEVERITY OF POSTOPERATIVE THYROTOXICOSIS

Although 37 of the 190 patients had thyrotoxicosis after the operation, they all showed symptomatic improvement with one exception (in

TABLE 1.—*Incidence of Postoperative Thyrotoxicosis by Years*

Year	Patients Followed	Patients Thyrotoxic after Operation	Patients Thyrotoxic after Operation, per Cent
1923	18	4	22.2
1924	28	4	14.3
1925	40	5	12.5
1926	37	6	16.2
1927	22	4	18.2
1928	45	14	31.1
Totals	190	37	
Average incidence of postoperative thyrotoxicosis			19.5

case 6397, chart 10). The postoperative thyrotoxicosis was mild in 56.8 per cent of the cases, moderately severe in 35.1 per cent and severe in 8.1 per cent; whereas in the same cases before operation the thyro-

1. We (Thompson, W. O., and Thompson, P. K.: Low Basal Metabolism Following Thyrotoxicosis: I. Temporary Type without Myxedema, with Special Reference to the Rôle of Iodine Therapy, J. Clin. Investigation **5**:441, 1928) previously reported the cases of a few patients who showed increased nervousness and slight tachycardia, palpitation and tremor in spite of a normal basal metabolism, and in whom these signs and symptoms disappeared when iodine was administered and the basal metabolism dropped to a subnormal level. When the basal metabolism was low the patients appeared healthy and no myxedema could be detected. However, since in these patients the evidence on which the diagnosis was based may be questioned, we have not considered them thyrotoxic in this study, with the exception of the patient in case 1812 (chart 3) in whom the basal metabolism eventually rose as high as plus 19 per cent when iodine was not being administered, and in whom there was no doubt about the presence of the disease. In other words, while we are well aware that the intensity of the thyrotoxicosis and the amount of elevation of the basal metabolism do not necessarily parallel one another, we felt that we should include in our criteria for the presence or absence of thyrotoxicosis one objective symptom that could not be questioned, that is, a persistently elevated rate of basal metabolism.

Patient			Basal Metabolic Rate at Time of Admission to Hospital, per Cent Normal	Last Basal Metabolic Rate Before Operation, per Cent Normal		Basal Metabolic Rate at Time of Discharge from Hospital, per Cent Normal	Summary of Post-Discharge Basal Metabolic Rates
Laboratory Number	Initials and Sex	Age at Time of Operation, Years			Surgeon		
1812	Mr. J. W.	39	+ 52	+44	Unknown	+ 9 (10)	See chart 3
1915	Mr. F. L.	43	+ 67	+53	C	+36 (13) +15*(26)	See chart 5
2031	Mrs. R. S. C.	34	+ 58	+15*	B	+48*(7)	+32 (88), +42 (205), +25 (426), +1* (459), +19* (524) pregnant, +37 (1360), +12* (1376), +7* (1403), +9 (1416), +6 (2093)
2077	Mrs. K. T.	24	+ 71	+25*	B	+17*(10)	+38 (49), +22 (200), +15* (231), x-rays, +37 (298), +22 (357), x-rays, +8 (378), —1 (1597), —5* (1688), +26* (taking desiccated thyroid [1759])
2375	Mr. O. G.	29	+ 37	+19*	A	—11*(8)	See chart 8
2524	Miss F. B.	39	+ 59	+29*	A	+ 6*(8)	+20 (107), +8 (190), +9 (280), +2 (394), +20 (582), +33 (645), +8* (669)
2632	Miss G. A. O.	18	+ 40*	+31*	A	+ 5*(11)	+37 (77), +38 (258), +9* (349), +38 (524), +32* (583), +35* (604), left hemithyroidectomy (607), +24 (1662), +17* (1685), +14* (1825)
2759	Mrs. A. P.	36	+ 40*	+25*	B	+10*(9)	+51 (58), +25 (92), +18* (123), +44 (167), x-rays, +42 (211), +36* (241), +63* (394) in hospital, +8* (403), second subtotal thyroidectomy (407), +1* (424), +28 (458), +29 (657), +9* (687), +3* (802), +27* (849), +16* (914), —4* (1039), —12* (1511), +5 (1649), —4 (1767)
3016	Mrs. N. P.	44	+ 60	+12*	G	—10*(13)	+12* (46), +23 (145), +31* (173), +12* (202), +19* (754), +29 (1404), +9* (1453), +19* (1540), x-ray, +29 (1587)
3187	Mrs. M. L. P.	54	+ 80	+22*	G	+16*(9)	—7* (40), +1* (103), +21 (142), +27 (253), +16* (289), +22* (491), +32 (527), x-rays, +12 (610), +35 (735), +16* (751), +10* (775), +16 (787), +19 (880), +11* (923), +23 (1003), +13* (1031), +9* (1108), +13* (1443)
3260	Miss B. S.	18	+119	+42*	A	— 2*(10)	+5* (39), +22* (175), +15* (263), +34 (354), +34 (362), x-rays, +14 (423), +8 (606), +34 (671), +30 (804) +9* (920), 0* (1340)
3437	Mr. C. V.	15	+ 53	—11*	B	+20*(10)	+30 (30), +8* (44), +45* (87), +44* (100), +62 (142) in hospital, +49* (154), second subtotal thyroidectomy (157), +1* (164), +40 (205), +10* (220), +39* (277)
3477	Mrs. M. C. S.	31	+ 64	+26*	A	+ 8*(7)	See chart 9
3867	Mrs. E. H.	30	+ 45	+20*	K	+ 5*(8)	+3* (38), unquestionably toxic (453)
3913	Mrs. M. R.	23	+ 54	+31*	A	+21*(7)	See chart 4
3961	Mrs. C. N.	29	+ 62	+21*	E	+19*(10)	+47 (72), +52* (87), +24* (179), +38 (198), x-rays, +48 (282), +7* (305), —3* (373), +22 (392), +23 (448), +5* (462), —3* (644), —1* (815), —22 (848), —2 (1072)
3967	Miss B. P.	15	+ 45	+ 9*	G & H	+ 5*(8)	+13 (38), +24 (166), +16 (171), +1* (185), +2* (193), +14 (218), —10* (290), +15 (613), +35 (783), +16 (874), + 15* (916)
4353	Mrs. M. G.	43	+ 47	+22*	D	+16*(7)	+45 (738), +27* (762), +41* (837), +32* (870) in hospital, second subtotal thyroidectomy (871), +1* (878), —23* (958), —22 (972)
4421	Miss W. McL.	21	+ 39	+ 3*	H	— 6 (8)	+13 (29), +24 (171), —5* (188), —4 (195), +17 (209), +24 (739)
4530	Mr. M. C.	48	+ 44*	+34*	B	+ 7*(8)	+21* (36), +22 (366), +43 (653), +19* (695), +24* (818)
4694	Miss E. F.	28	+ 99	+34*	A	— 7*(10) +16 (25)	+2* (64), +27 (150), +20 (151), —3* (189), —4* (273), —5* (517)
5168	Mrs. E. H.	26	+ 81	+26*	B	+ 6*(13)	+37 (36), +25 (64), +8* (84), +17* (148), +8* (200), +45 (231), +43 (235), +6* (263), +18* (380), +7* (503)
5193	Mrs. V. P.	42	+ 64	+42*	A	+25*(8)	+13* (52), +27 (88), +26 (162), +16* (190), +9* (245), +8* (435), +19 (505), +28 (581)
5203	Miss A. W.	22	+ 51	+52*	I	+28*(8)	+35 (41), +33 (131), +16 (364), —2* (378), +5* (399), +20 (435), +27 (470), +15* (505), +27 (569)
5272	Miss E. M.	35	+103	+25*	D	+21 (14)	See chart 2
5581	Miss V. G.	18	+ 80	+42*	A	+ 9*(8)	See chart 7
5596	Mr. H. E.	33	+ 54	+27*	B	+ 9*(25)	+34 (49), +27 (97), +23* (127), +41 (194), +13* (216), +27* (279), x-ray, +31* (385), +29* (419)
5640	Mrs. M. F. B.	40	+ 36	+ 1*	B	—11*(10)	+40 (46), +30 (100), 0* (125), +18* (212)
5767	Mrs. J. P.	48	+ 88	+38*	J	+11*(10)	+42 (54), +30* (150), +7* (367), +17 (423)
5944	Mr. P. M.	42	+ 63	+41*	J	+36*(11)	+9 (78), +34 (162), +42 (288), +19* (316)
5957	Mrs. M. B.	37	+ 90	+28*	D	+17*(13)	+45 (53), +24* (60), +24* (147), +37 (179), +44 (188), +13* (209), +53 (248), +22* (328), +27* (360)
5995	Miss M. A. P.	17	+ 35	+13*	E	— 7*(10)	+25 (47), +19 (54), +19* (83), +15* (185), +37 (206), +29 (210), +15* (231), +21* (321)
6102	Mr. J. C.	40	+ 64	+65*	D	+20*(8)	+33* (49), +32* (75), +53 (106), +16* (148), +15* (183)
6125	Mrs. M. E. M.	23	+ 33	+14*	F	0*(8)	+23 (79), +12* (110)
6248	Mrs. M. C.	25	+ 71	+35*	A	+23*(7)	+42 (50), +32 (76), +41 (147)
6376	Miss E. S.	21	+ 81	+26*	F	+ 4*(10)	+15* (26), +11* (55), +23 (98), +30 (140), +27* (186), +18* (220)
6397	Miss K. R.	26	+ 42	+15*	F	+ 3*(11)	See chart 10

† This table gives only an outline of the basal metabolic rates. In most instances, many more determinations were done. The figures in parentheses denote the number of days after operation.

* Medication with iodine.

toxicosis was mild in 5.4 per cent, moderately severe in 43.2 per cent and severe in 51.4 per cent. All of the patients resumed their usual occupations following operation, although under more or less of a handicap according to the severity of the symptoms. A summary of the determinations of the basal metabolism made in the 37 patients who were thyrotoxic following operation is given in table 2.

In 24 of the 36 patients who improved, the basal metabolism was considerably lower without medication after operation than before preoperative treatment with iodine was begun. In 3 cases (cases 2632, 2759 and 4530) it was not possible to make this comparison because no determinations of basal metabolism had been made before the administration of iodine preceding operation, and in one case (case 3867) because no determination was made after operation at a time when iodine was not being administered. In 3 of 6 cases (cases 2375, 3437 and 4353) showing no reduction in the basal metabolism at times when the patient was not taking iodine after operation, and in 3 cases (cases 1915, 5596 and 6102) in which little reduction was noted, there was general improvement with gains in weight ranging from 3 to 7 Kg. Similar improvement with gain in weight but no reduction in basal metabolism was noted by Porter [2] following a hemithyroidectomy. Considering the 37 cases as a whole, the basal metabolism at the time of admission to the hospital averaged about plus 64 per cent, and after operation, when no iodine was being administered, it averaged about plus 40 per cent.[3]

CLASSIFICATION OF POSTOPERATIVE THYROTOXICOSIS ON THE BASIS OF TIME OF ONSET

It is important to determine whether the disease disappears after operation and then recurs, or whether it merely persists. The thyrotoxicosis was considered persistent when there was no evidence to show that it had disappeared temporarily at any time after operation except under the influence of iodine. The thyrotoxicosis was considered recurrent only when there was evidence to show that there was a period after operation when, without medication, it was not present. On this basis, 35 of the 37 patients had persistent and only 2 recurrent thyrotoxicosis. In one of these definite recurrences (case no. 2524) the

2. Porter, C. A.: Analysis of My End-Results in Thyroid Surgery, Surg. Gynec. Obst. **36**:621, 1923.

3. In each instance, omitting cases 2632, 2759, 3867 and 4530 in which no comparisons could be made, the figure used was the highest postoperative rate of basal metabolism during a period in which there was no treatment with iodine.

onset was between thirteen and nineteen months after operation, and in the other (case no. 1812), between five and one-half months and three and one-half years after operation (this patient was normal until five and one-half months after operation, but was not seen again until three and one-half years after operation, at which time thyrotoxicosis was present). Of the 35 patients in whom apparent persistences were observed, the high basal metabolism was first noted: in 15 cases, within two weeks after operation, usually at the time of discharge from the hospital; in 4 cases, between two weeks and one month after operation; in 10 cases, between one and two months; in 3 cases, between two and three months; in 2 cases, between three and four months, and in 1 case, between one and eight months.

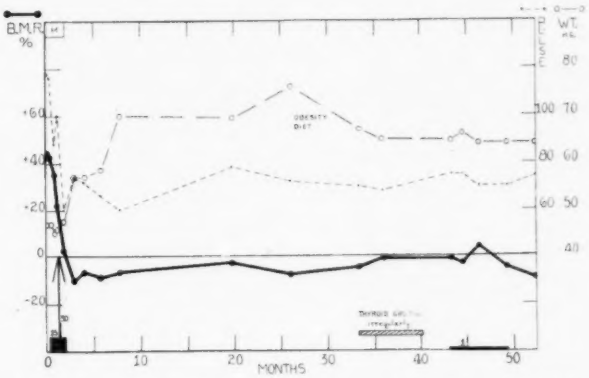

Chart 1 (lab. no. 3094).—The usual course of the basal metabolism, pulse and weight in a case of exophthalmic goiter cured by one subtotal thyroidectomy. Note that following operation the basal metabolism promptly dropped to normal and remained there. In this and subsequent charts, *H* denotes a period of hospitalization; the arrows denote subtotal thyroidectomies; the half-arrows, hemithyroidectomies; the black areas, periods of treatment with compound solution of iodine; the figures above them, the daily doses in drops, and the cross-hatched areas, periods of treatment with desiccated thyroid.

In the 20 cases of persistence in which the high basal metabolic rate was first noted later than two weeks after operation, there were usually a few intervening normal metabolic rates (table 2), but these were obtained while the patient was taking iodine. This medication with iodine renders it impossible to tell definitely whether or not these patients had a spontaneous brief interval of freedom from the disease. The prompt rise in the basal metabolism, however, after the omission of iodine, together with the presence of palpable thyroid tissue before its omission in many cases, makes it appear highly probable that such

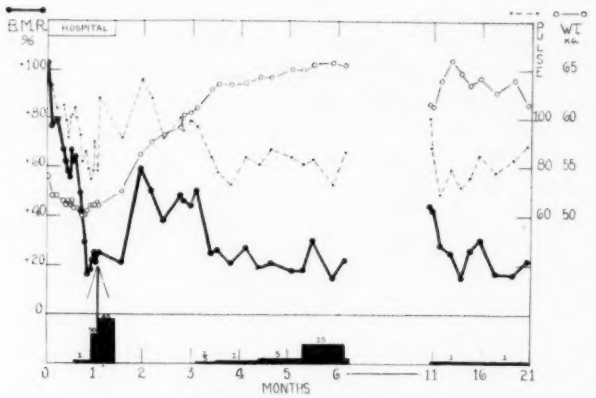

Chart 2 (lab. no. 5272).—Typical persistence of exophthalmic goiter following a subtotal thyroidectomy, showing the course of the basal metabolism, pulse and weight. Note that the level of the basal metabolism when iodine was not being administered was about the same ten months after operation as from one to two months after operation, and that the level to which it was depressed by iodine was the same twenty months after operation as two weeks after operation. This chart also shows that iodine may hold the basal metabolism at a constant level for many months.

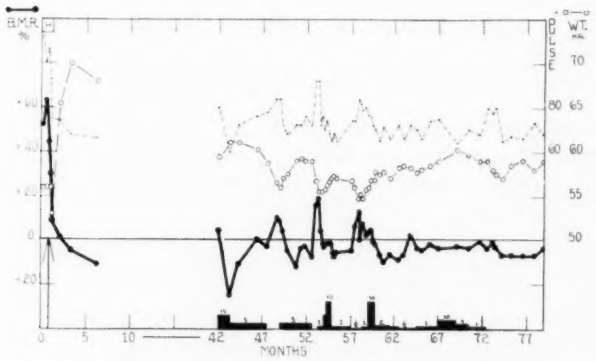

Chart 3 (lab. no. 1812).—Recurrence of exophthalmic goiter in association with regeneration of thyroid tissue, after the disease had been absent for at least five and one-half months following a subtotal thyroidectomy; and control of this thyrotoxicosis by iodine until it and the palpable thyroid tissue disappeared.

was not the case. In any event, there were only 3 patients in whom the time of onset of the postoperative thyrotoxicosis was obscured for more than three months.

Data from a typical case in a patient who showed no postoperative thyrotoxicosis, in one with a typical persistence and in one with a typical recurrence are recorded in charts 1, 2 and 3, respectively.

In table 3 are contrasted the basal metabolic rates at the time of discharge from the hospital and during iodine administration of the 37 patients who were thyrotoxic following operation and 37 patients selected at random from the 153 who were not thyrotoxic following

TABLE 3.—*Comparison of Basal Metabolic Rates During Administration of Iodine Shortly After Operation in Patients Who Were Thyrotoxic and in Those Who Were Not* *

Basal Metabolic Rate, per Cent Normal	Patients Not Thyrotoxic after Operation	Patients Thyrotoxic after Operation
+30 or over	..	2
+25 to +29	..	2
+20 to +24	..	5
+15 to +19	..	6
+10 to +14	2	2
+ 5 to + 9	6	10
0 to + 4	6	3
— 5 to — 1	8	2
—10 to — 6	14	3
—15 to —11	1	2
Total	37	37

* In the thyrotoxic group, one patient in the +20 to +24 division and another in the —10 to —6 division had omitted iodine for four and five days, respectively, before the observation was made. These are inadequate lengths of time for the effect of iodine to wear off. One patient in the +5 to +9 group did not have any iodine during the period of hospitalization, but the basal metabolism certainly would not have been any higher than this on iodine.

operation. Whereas in 15 (40.5 per cent) of the 37 patients who were thyrotoxic following operation, the basal metabolism was plus 15 per cent or higher at the time of discharge (usually from ten to fourteen days after operation) when iodine was being administered, in no case in the other series was it as high as plus 15 per cent under these conditions. In only 7 (19 per cent) of the thyrotoxic cases was it lower than 0 at the time of discharge, as compared with 23 (62 per cent) of the nontoxic patients. Although the data are not extensive enough to warrant definite conclusions, a similar situation appears to have existed in the patients undergoing subtotal thyroidectomy in the days before iodine was used, except that the basal metabolism in those that remained thyrotoxic did not return to normal until the disease disappeared spontaneously.

DURATION OF POSTOPERATIVE THYROTOXICOSIS

Duration of Persistences.—In the five cases in which after a more or less protracted interval of iodine therapy iodine could be omitted for several months without the recurrence of symptoms, it was possible to estimate the duration of the postoperative thyrotoxicosis as follows: in case 2031, from three and three-fourths to four years; in case 2759, from two and one-half to three and one-sixth years; in case 3913 (chart 4), from one and one-half to two and two-thirds years; in case 3961, from one and one-fourth to two and one-fourth years, and in case 2077, 1 year; the average was from two to two and one-half years. It is to be noted that the duration may have been shortened by roentgen treatment in case 3961 and in case 2077, and by roentgen treatment followed by another subtotal thyroidectomy in case 2759. In

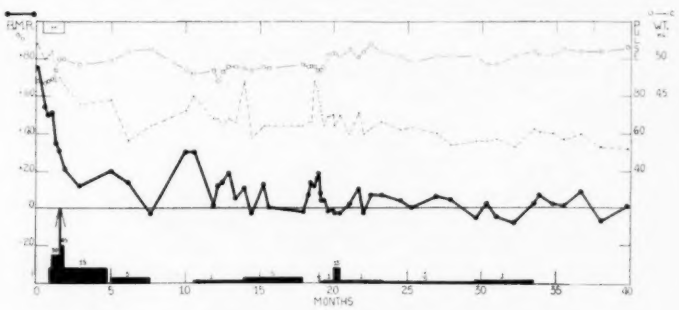

Chart 4 (lab. no. 3913).—Control of persistent thyrotoxicosis by iodine until the disease disappeared. The disease was mild after operation and iodine held the basal metabolism at a standard normal level, in contrast to cases illustrated in charts 2, 7 and 9, in which it held it at a higher level.

these cases iodine was administered for protracted periods after operation.

In cases in which the basal metabolism was still high and there was clinical evidence of thyrotoxicosis at the time the patient was last seen, or in which the basal metabolism was normal and the patient was apparently well but was taking iodine, one can merely state the minimum time the patient was known to have had thyrotoxicosis after operation. In this respect, the remaining 30 cases may be grouped as follows: Thyrotoxicosis was present after subtotal thyroidectomy for at least from three to five months in 3 cases, from six to eleven months in 8, from twelve to twenty-three months in 10, from twenty-four to thirty-five months in 4, from thirty-six to forty-seven months in 1, from forty-eight to fifty-nine months in 1 and from sixty to seventy one

months in 3. While in the 5 cases in which it was possible to estimate the duration, the disease had disappeared within from one to four years after operation, its disappearance was apparently hastened by additional treatment in 3 of these, and the foregoing data show that it may often persist longer than this, for from four to six years, if not more, in at least 13 per cent of the cases (chart 5).

Duration of Recurrences.—In case 2524 the duration of the recurrence was unknown. The patient was observed for only two months without medication at the time the disease recurred.

In case 1812 (chart 3), the patient was free from symptoms and showed a normal metabolism for six months after iodine was last omitted. The recurrence lasted at least for from one to two and one-

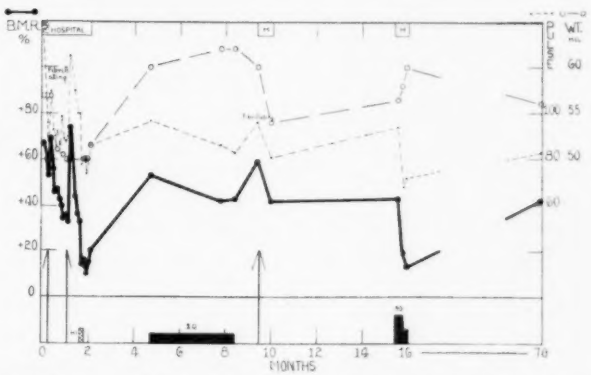

Chart 5 (lab. no. 1915).—Prolonged persistence of exophthalmic goiter and regeneration of thyroid tissue in spite of two hemithyroidectomies and one subtotal thyroidectomy for exophthalmic goiter.

half years while the patient was under observation, in addition to the unknown length of time it was present during the three year hiatus before he returned to the clinic for treatment.

SCHEMATIC REPRESENTATION OF PERSISTENCES AND RECURRENCES

From the foregoing data it is possible to construct a schematic representation of the various courses of the basal metabolism following subtotal thyroidectomy for exophthalmic goiter (chart 6). If no iodine is administered, the metabolism in the first few days after operation may drop from a point *B* to a point *C*. Then it may follow any one of several courses. If a cure results, it follows the line *CYO*. If the disease persists, the metabolism may follow any course between *CDO* and *CEDO*; that is, it almost never reaches a standard normal level until the disease disappears. If the metabolism drops much below the

line CD and then rises, some regeneration of thyroid tissue can often be observed when it does rise. If the usual short, preoperative and postoperative courses of iodine are given, the metabolism may drop from a point A to a point X before operation. Then, if a cure results from thyroidectomy, it will follow the line XYO. If the disease persists, the course of the metabolism may lie anywhere between the lines XDO and $XYDO$; that is, it usually drops somewhat immediately after the operation, occasionally to a standard normal level. The subsequent rise usually follows the omission of iodine, and the line DO is intended to show the course of the metabolism when no iodine is being administered. If a recurrence takes place, then at any point P in the line YO (the line YP usually covering at least several months) the metabolism

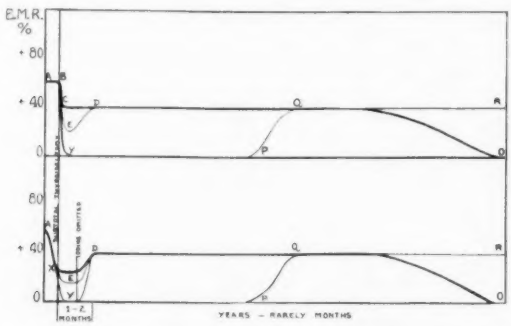

Chart 6.—Schematic course of the basal metabolic rate in persistence and recurrence of exophthalmic goiter, in patients who do not receive iodine (upper half of chart) and in those who do receive it for a short period before and after subtotal thyroidectomy (lower half of chart).

rises and may follow any course PQO. The line DQ has been extended to R to allow for occasional cases in which the disease seems to last indefinitely.

Several variations of the courses described may be noted; for example, the severity of the thyrotoxicosis following operation, as measured by the height of the rate of basal metabolism, varies considerably from patient to patient.

CAUSE OF POSTOPERATIVE THYROTOXICOSIS

Miscellaneous Factors.—It may be seen from tables 4 to 6 that the average age, age limits, age distribution, sex distribution and duration of the disease at the time of operation were about the same in the toxic as in the nontoxic group. Not only was the average initial basal metabolic rate roughly the same in the two groups of patients, but the

level to which iodine depressed the rate of basal metabolism before operation was also roughly the same in both. A somewhat higher percentage of cases in the postoperative toxic group was found to have an initial basal metabolism of plus 60 per cent or over, a markedly

TABLE 4.—*Age of Patient at Time of Operation*

Age	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Under 20 years	5	13.5	19	12.5
20 to 29 years	13	35.2	36	23.7
30 to 39 years	9	24.3	46	30.3
40 to 49 years	9	24.3	39	25.6
50 to 59 years	1	2.7	11	7.2
60 years or over	0	0.0	1	0.7
	37		152	
			1 unknown	
Average age	30.5 years		30.6 years	
Oldest	54 years		68 years	
Youngest	15 years		14 years	

TABLE 5.—*Sex of Patient*

Sex	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Male	9	24.3	34	22.2
Female	28	75.7	119	77.8
	37		153	

TABLE 6.—*Duration of Disease at Time of Operation*

Duration	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Six months or less	11	29.7	52	34.0
Between six months and one year	11	29.7	47	30.7
Between one year and two years	4	10.8	23	15.0
Over two years	10	27.0	21	13.7
Unknown	1	2.7	10	6.6
	37		153	
Shortest duration	1 month		3 weeks	
Longest duration	5 years		15 years	
Average duration	18.8 months		18.7 months	

enlarged thyroid before operation, and a bruit [4] over the gland before operation (tables 7 to 9). Apart from these slight differences, there were no definite distinctions between the two types of patients.

4. It is of interest that in patients who are thyrotoxic following a thyroidectomy, a bruit over the thyroid is less common than before operation, owing, no doubt, to the changes in blood supply resulting from the operation.

TABLE 7.—*Basal Metabolic Rate on Admission to Hospital*

Basal Metabolic Rate,* per Cent Normal	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Below +40	7	18.9	39	25.5
+40 to +49	7	18.9	38	24.8
+50 to +59	7	18.9	31	20.3
+60 or over	16	43.3	45	29.4
	37		153	
Highest	+119 per cent		+102 per cent	
Lowest	+ 33 per cent		+ 15 per cent†	
Average	+ 58 per cent		+ 51 per cent	

* In a few cases this was during the administration of iodine.
† During the administration of iodine.

TABLE 8.—*Size of Thyroid Gland Before Operation (Incomplete)*

Size of Thyroid Gland	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Not enlarged	0	0.0	4	3.4
Slightly enlarged	5	15.2	21	18.1
Moderately enlarged	22	66.6	82	70.7
Markedly enlarged	6	18.2	9	7.8
	33		116	

TABLE 9.—*Bruit Over Thyroid Gland Before Operation (Incomplete)*

	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Bruit	33	100.0	93	80.2
No bruit	0	0.0	23	19.8
	33		116	

TABLE 10.—*Amount of Thyroid Tissue Palpable After Operation*

	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Note was made in	35		104	
Palpable tissue absent	1	2.9	45	43.3
Palpable tissue present	34	97.1	59	56.7
Questionable amount	4	11.4	26	25.0
Definite amount	17	48.6	28	26.9
Considerable amount	13	37.1	5	4.8

Palpable Thyroid Tissue After Operation.—In most of the cases of postoperative thyrotoxicosis palpable thyroid tissue was present. The amount was estimated rather roughly by palpation, and is expressed in table 10 by the terms questionable, definite and considerable. In the "questionable" cases the thyroid tissue was sufficiently difficult to palpate to render its presence open to question. In the "definite" cases the thyroid tissue could be felt without difficulty and varied in amount up to 1.5 cm. in diameter. The "considerable" cases included all those in which there was a mass of 1.5 cm. in diameter or larger. Within the first one to two months after operation, palpation is often not especially valuable because of the induration about the scar. In many instances a definite amount of palpable tissue probably did not represent regeneration, but simply the tissue left by the surgeon; nevertheless there was unquestionably regeneration in many of the patients with a "considerable" amount of tissue. In some of the patients the amount of palpable tissue increased in size during observation. This regeneration began shortly after operation and did not represent a true recurrence, but simply an effect of the persistence of the cause of the disease. A small amount of tissue could be felt in many of the postoperative nontoxic cases as well as in the toxic cases, but a "considerable" amount was almost always associated with thyrotoxicosis. Thyrotoxicosis without palpable thyroid tissue is occasionally encountered following thyroidectomy, but it is rare in our experience, only one mild case (case 3187) being noted in this series.

Amount of Tissue Left in at Operation.—The amount of tissue left in at operation was practically impossible to determine with any degree of accuracy, as in many cases the surgeon did not attempt to state in his operative notes the fraction removed, calling the operation simply a "subtotal thyroidectomy"; and even in cases in which the fraction was expressed, it was admittedly only a rough approximation. Therefore, instead of attempting to tabulate the amount of tissue left in situ, we tabulated the results of the individual surgeons in table 11. It may be noted that the combined results of the three surgeons who had performed the greatest number of thyroidectomies are definitely better than the combined results of ten other surgeons, each of whom had performed relatively few thyroidectomies. The percentage of cases of postoperative thyrotoxicosis was 14.4 for the first three surgeons and 36.3 for the ten others. We know from observation that the three surgeons who had the smallest incidence had performed more complete thyroidectomies than the others. It is fairly evident that experience in performing the operation is an important factor in preventing postoperative thyrotoxicosis.

Preoperative and Postoperative Administration of Iodine.—One of the surgeons had the impression that postoperative thyrotoxicosis has become much more common since the preoperative use of iodine. Consequently, in table 12 we have compiled the data on the patients undergoing subtotal thyroidectomy before this medication came into vogue.

TABLE 11.—*Incidence of Postoperative Thyrotoxicosis According to Surgeons*

Surgeon	Patients Operated On	Patients Thyrotoxic After Operation	
		Number	Per Cent
A	85	11	12.9
B	42	8	19.0
C	19	1	5.3
D	10	4	40.0
E	8	2	25.0
F	8	3	37.5
G	5.5	2.5	45.4
H	4.5	1.5	33.3
I	3	1	33.3
J	2	2	100.0
K	1	1	100.0
L	1	0	0.0
Unknown	1	0	0.0
All surgeons	190	37	19.5
Surgeons A, B and C*	146	20	13.7
The remaining 10 other surgeons	44	17	38.6

* C, a thyroid surgeon, who retired shortly after the present study began, had done a large number of thyroidectomies before 1923.

TABLE 12.—*Incidence of Thyrotoxicosis Following Subtotal Thyroidectomy Before 1923,* According to Surgeons*

Surgeon†	Patients Followed for 3 Months or More After Operation	Patients Thyrotoxic After Operation	
		Number	Per Cent
C	21	*4	19.1
A	19	2	10.5
K	1	1	100.0
Totals	41	7	
Average incidence			17.1

* That is, before the use of iodine.
† If tables 11 and 12 are combined, the percentages of recurrences for A and C are equal.

As may be seen, the percentage of postoperative thyrotoxicosis before the days of the use of iodine was 17.1 as compared with 19.5 since the introduction of iodine. The majority of the foregoing operations were performed by two of the three surgeons (A and C) who now have the smallest number of persistences. It appears, therefore, that preoperative medication with iodine is not a determining factor.

Practically all of the patients received iodine postoperatively for at least a week, that is, until discharge from the hospital, and many of

them received it continuously for several weeks thereafter. Many others received it intermittently shortly after discharge. In some of the toxic cases the postoperative thyrotoxicosis was first evident only after a continuous postoperative course of iodine for from one to four months had been omitted, although its presence often seemed obvious before this because of the large amount of palpable thyroid tissue. In most of the other toxic cases, it was evident at the time of the first postoperative basal metabolism determination, in spite of treatment with iodine. Thus the postoperative administration of iodine does not prevent the occurrence of thyrotoxicosis nor the regeneration of thyroid tissue.

TREATMENT, INCLUDING THE RESPONSE TO IODINE

Most of the patients received iodine at least intermittently after operation. In 10 cases its use was not continued long enough to determine the patient's response. In 3 of the remaining 27 cases little or no reduction in basal metabolism was noted during its administration, and in 3 others, only a temporary reduction. In 18 of the remaining 21 cases the basal metabolism could be held at a more or less constant level for from months to years by continuous administration. In 11 of these the level to which iodine thus depressed the metabolism was plus 15 per cent or lower; in 6, from plus 16 to plus 20 per cent, and in 1 case, from plus 21 to plus 25 per cent.[5] In three cases the level to which iodine reduced the basal metabolism was somewhat inconstant and ranged between zero and plus 33 per cent. In general, the signs and symptoms of the disease in patients in whom iodine held the metabolism at a level of plus 15 to plus 25 per cent were only slight. In all cases showing only temporary improvement or none during the administration of iodine, there was a large amount of palpable thyroid tissue. Various types of response to iodine are shown in charts 2 to 5 and 7 to 10.

In 6 cases a second operation was performed, with varying degrees of relief (usually complete). A second operation was recommended in 4 other cases; in 3 it was refused and in the fourth it is to be done soon. Roentgen treatment was given in 7 cases, with some improvement in 5.

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5. The fact that in fifteen of the patients who were thyrotoxic following operation the basal metabolism was plus 15 per cent or higher during the administration of iodine at the time of discharge from the hospital (table 3) is directly related to the fact that in at least an equal number of patients, iodine did not hold the rate of basal metabolism constantly below plus 15 per cent after discharge. In a few patients, the level at which iodine held the basal metabolism was a little higher following than at the time of discharge. This slight rise could be attributed to the elimination of rest, to a diminution in the effect of iodine or to an increase in the severity of the disease. All three were probably factors.

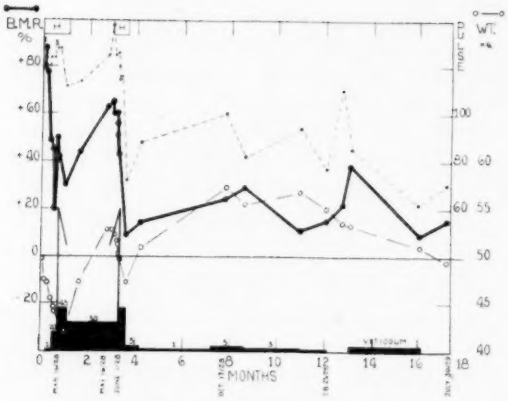

Chart 7 (lab. no. 5581).—Failure of two extensive hemithyroidectomies to reduce the basal metabolic rate to normal in a case of exophthalmic goiter. There was marked regeneration of thyroid tissue following each operation. The thyrotoxicosis was controlled for fairly long periods by iodine.

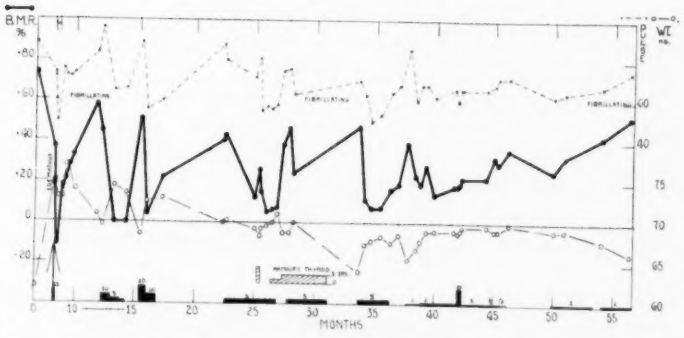

Chart 8 (lab. no. 2375).—Progressive, but gradual (years) increase in the level to which iodine depressed the high basal metabolism that persisted following a subtotal thyroidectomy for exophthalmic goiter. Some of this increase may be accounted for by a rather marked regeneration of thyroid tissue.

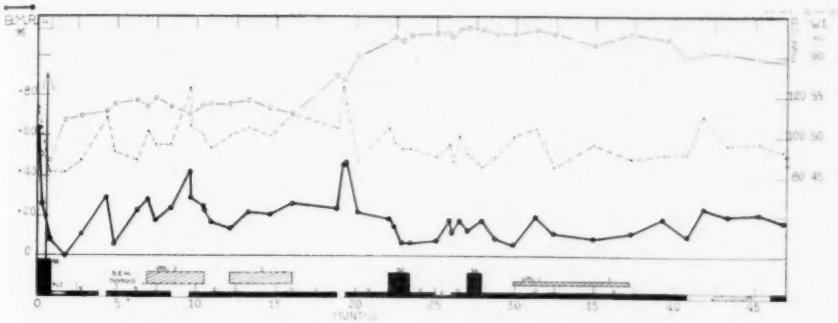

Chart 9 (lab. no. 3477).—Typical persistence of exophthalmic goiter after subtotal thyroidectomy, with control of the thyrotoxicosis by iodine continuously for four years after operation, except during three short omissions of that medication. The patient married and was able to do housework and private nursing during the period of observation, but some symptoms and signs of the disease were present, in addition to a large amount of palpable thyroid tissue. A second operation was therefore advised, and the patient finally consented.

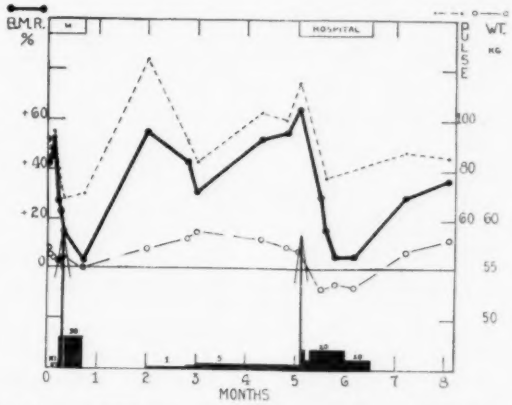

Chart 10 (lab. no. 6397).—Typical persistence of exophthalmic goiter in spite of two subtotal thyroidectomies, with only temporary improvement during the administration of iodine. Marked regeneration of thyroid tissue was noted following each operation.

RESULTS OF SUBTOTAL THYROIDECTOMY FOR EXOPHTHALMIC GOITER IN VARIOUS CLINICS

The type of follow-up that includes both physical examination and the determination of the basal metabolism at fairly frequent intervals is essential to procure accurate information regarding the results of subtotal thyroidectomy for exophthalmic goiter. Unfortunately, many of the reports in the literature of the percentage of cures obtained with this form of treatment are based on a follow-up by letter or by one physical examination, and sometimes only on the condition of the patient at the time of discharge from the hospital. Such reports are prone to show too high a percentage of cures. Similar methods applied to our series would indicate fewer toxic cases. It is remarkable in some instances how consistently high the basal metabolism may be after operation (about plus 40 per cent) and yet be associated with signs and symptoms of only mild thyrotoxicosis (in cases 5272 [chart 2] and 5944). Such patients often have few subjective symptoms and gain considerable weight, yet there are definite signs of the persistence of the disease that can be detected by careful observation.[6] Richter[7] remarked on the cases of 6 such patients in his series, who, in their own estimation, might have been reported as cured. Then, if we had seen our patients only once several years after operation, some of the cases in which the disease persisted for a time and then disappeared would have been missed. Figures based on the condition of the patient a week or two after operation would be almost worthless, because our patients, according to the routine followed in most clinics, were given iodine during the postoperative period in the hospital, which lasted about two weeks.

Elliott,[8] in 1926, from the Wesley Memorial Hospital, Chicago, reported on the recalling of 100 patients with hyperthyroidism (including 62 with exophthalmic goiter) on whom subtotal thyroidectomy had been performed from six months to six years before the recall. The rate of basal metabolism was determined in 72 cases. In 50 it was normal, in 9 it was minus 10 per cent or lower, and in 13 it was plus 10 per cent or higher. However, of the 70 who considered themselves

6. Careful questioning and observation show that such patients present some or all of the following signs and symptoms: increased nervousness, emotional instability, insomnia, increased perspiration, palpitation, tachycardia and tremor. Compared with their preoperative state, the improvement in these patients is sometimes so marked that they consider themselves well. After treatment with iodine, however, they usually notice a further marked improvement.

7. Richter, H. M.: Thyroidectomy: Its Relation to the Cure of Thyrotoxicosis, J. A. M. A. **88**:888 (March 19) 1927.

8. Elliott, C. A.: The Control of Hyperthyroidism by Thyroidectomy: Results in One Hundred Cases, J. A. M. A. **89**:519 (Aug. 13) 1927.

well, in 23 it was three months after the operation, in 21 within six months and in 14 after from one to three years. Only 4 patients in the whole series were considered to have thyrotoxicosis. Richter,[7] of Chicago, in 1927 reported the results of "thyroidectomy" (evidently subtotal) in 100 cases of toxic goiter, of which 76 were of the exophthalmic type. The duration of the follow-up was not given. In 6 cases there was a persistently high rate of basal metabolism after operation and a second thyroidectomy was required. The same author more recently [9] reported only "one definite failure to secure normal metabolism in 447 consecutive patients that were available for study." Frazier and Mosser,[10] of Philadelphia, in 1928, reported a series of 100 cases of exophthalmic goiter "thoroughly followed" on a five-year plan in which a physical examination was attempted four times the first year, twice the second year and once yearly thereafter. Some patients who lived far away reported by letter. The thyroidectomy was usually subtotal. Several basal metabolic rates were determined but not reported. On the basis of an average postoperative interval of ten months, they said that 71 per cent of the patients were entirely well, 19 per cent had residual nervous symptoms but no hyperthyroidism, 6 per cent had "visceral changes" but no hyperthyroidism, 1 per cent had "persistent hyperthyroidism" unrelieved by operation and 4 per cent had "recurrent hyperthyroidism." While Pemberton [11] recently estimated the incidence of postoperative thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter at the Mayo Clinic as "certainly not more than 5 per cent," he realized that "the accuracy of any estimate of incidence would depend chiefly on the thoroughness and number of examinations and the interval elapsing since the operation." [12] Jordan,[13] in 1925, at the

9. Richter, H. M.: Thyroidectomy, Surg. Gynec. Obst. **49**:67, 1929.

10. Frazier, C. H., and Mosser, W. B.: End-Results from the Surgical Treatment of Hyperthyroidism, J. A. M. A. **90**:657 (March 3) 1928.

11. Pemberton, J. deJ.: Recurring Exophthalmic Goiter: Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, J. A. M. A. **94**:1483 (May 10) 1930.

12. The statistics of Judd (Results of Operations for Adenoma with Hyperthyroidism and Exophthalmic Goiter, Ann. Surg. **72**:145, 1920) and of Pemberton (The End-Results of Surgery of the Thyroid Gland, Arch. Surg. **7**:37 [July] 1923) from the Mayo Clinic, based on a follow-up by letter of patients operated on in 1914 and 1916, respectively, and giving figures of 5.6 per cent and 11 per cent, respectively, for the incidence of postoperative thyrotoxicosis, are not directly pertinent here, as the type of operation varied greatly. Pemberton made statements regarding the interval histories of the patients, which suggest that the incidence a shorter time after operation may have been higher than 11 per cent. Mayo, in Keen's "Surgery" (Philadelphia, W. B. Saunders Company, 1921, vol. 8, p. 25), in speaking of the results of thyroidectomy, said that "in at least 10 per cent of simple and hyperplastic goiters operated on, there is some degree of recurrence." Ochsner, of Chicago (End-Results of Goiter Operations, Ann. Surg. **80**:388,

Lahey Clinic, noted that 6.7 per cent of their patients with exophthalmic goiter failed to show a normal basal metabolism six months after subtotal thyroidectomy. Smith, Clute and Strieder,[14] in 1928, at the same clinic, in following 100 cases of hyperthyroidism by physical examination and determinations of basal metabolism for one year or more after subtotal thyroidectomy observed 7 patients with persistence of the disease. Kessel and Hyman[15] of New York, in 1927, reporting results in 60 cases of exophthalmic goiter two years after subtotal thyroidectomy, said that 15 patients had marked exacerbations at one time or another after operation and 18 others had mild residual symptoms. In only 7, however, was the basal metabolic rate higher than plus 18 per cent at the last reading. Mason[16] of Seattle, in 1920, in a follow-up by letter in 42 cases of subtotal thyroidectomy for exophthalmic goiter, found a second operation necessary in 12 per cent. Waits,[17] in 1922, in a letter follow-up from one to six years after operation (usually subtotal) for exophthalmic goiter, said that 11 per cent of the patients who answered had a "slight return of goiter." One of the patients had a second operation. Brodersen and Harbitz,[18] in 1927, reported 87.4 per cent of the patients cured, 11.5 per cent improved and 1.1 per cent worse, from one to four years after subtotal thyroidectomy for exophthalmic goiter; 5.7 per cent had undoubted or questionable relapses. Ladwig,[19] in 1925, had good results in 21 of 35 cases, fair in 6

1924), on the basis of a follow-up by letter, reported an incidence of 24 per cent in a series operated on during the period from 1913 to 1923. Jackson (Goiter and Other Diseases of the Thyroid Gland, New York, Paul B. Hoeber, Inc., 1926, p. 242) said that the incidence of recurrences in his cases before the days of medication with iodine was 2 per cent. None of these writers, however, specifies the type of operation.

13. Jordan, S. M.: Basal Metabolic Rates and Their Relation to End-Results in Thyroid Disease: A Statistical Study, Arch. Surg. **11**:1 (July) 1925.

14. Smith, L. W.; Clute, H. M., and Strieder, J. W.: The Results in One Hundred Consecutive Cases of Hyperthyroidism Operated Upon, Surg. Gynec. Obst. **46**:325, 1928.

15. Kessel, L., and Hyman, H. T.: Exophthalmic Goiter and the Involuntary Nervous System: XVI. The Influence of Subtotal Thyroidectomy with and without Compound Solution of Iodine on the Course of the Disease, Arch. Int. Med. **40**:623 (Nov.) 1927.

16. Mason, J. T.: Mistakes in One Hundred Thyroidectomies, with Description of a New Method of Thyroid Cauterization in Treating Exophthalmic Goiter, J. A. M. A. **75**:160 (July 17) 1920.

17. Waits, C. E.: Preoperative and Postoperative Studies in Goiter, J. M. A. Georgia **11**:355, 1922.

18. Brodersen, N. H., and Harbitz, H. F.: Morbus Basedowii und Ergebnis seiner operativen Behandlung im Krankenhaus in Drammer, Acta chir. Scandinav. **61**:107, 1927.

19. Ladwig, A.: Nachuntersuchungen an Basedow-Operierten. Ein Beitrag zum Basedow-Problem, Arch. f. klin. Chir. **137**:367, 1925.

and poor in 8 (nearly 25 per cent), from one to thirteen years after subtotal thyroidectomy. Porter,[2] at the Massachusetts General Hospital in 1923, observed the basal metabolic rates in 28 of his 50 patients with toxic goiter on whom he had performed a subtotal thyroidectomy during the period between 1904 and 1921. In none was the basal metabolism above plus 10 per cent. It is to be noted, however, that some of these determinations of basal metabolism were made so long after operation that cases of temporary postoperative thyrotoxicosis may not have been detected. Thus Richardson,[20] also of the Massachusetts General Hospital, in 1923, in a one and one-half year follow-up which included physical examinations and determinations of the basal metabolism in 30 patients who had undergone subtotal thyroidectomy for exophthalmic goiter reported 5 cases (17 per cent) with postoperative thyrotoxicosis.

Thus it may be seen that the incidence of thyrotoxicosis after subtotal thyroidectomy for exophthalmic goiter, as given in the literature, ranges from about 0.25 to 25 per cent, many of the estimates falling in the vicinity of from 5 to 7 per cent. Our average of 19 per cent may appear high and give the impression that the end-results at the Massachusetts General Hospital have not been so good as those obtained elsewhere, owing perhaps to inadequate surgical measures. We are convinced that this does necessarily follow. From personal observation, we know that in some of the clinics from which the lower percentages have been reported the routine operation has been considerably less extensive than that carried out by the surgeons who have performed the most thyroidectomies at the Massachusetts General Hospital. The difference in incidence may be attributed in part to the manner in which the patients were followed. So far as clinical symptoms are concerned, our 37 postoperative toxic cases could be listed as follows: much improvement in 26 cases (70 per cent), moderate improvement in 10 cases (27 per cent) and no improvement in 1 case (3 per cent).

SCARCITY OF TRUE RECURRENCES

One outstanding feature of our study was the small number of recurrences, that is, cases in which the disease disappeared after operation and then recurred. In striking contrast to this conclusion was that of Pemberton [11] that most cases of postoperative thyrotoxicosis are recurrences and only a small number persistences. It is possible that this difference between the two conclusions may be attributed in part to the fact that Pemberton was unable to make frequent observations on his patients during the interval between the first and second operations. The marked predominance of persistences has been observed by Lahey and

20. Richardson, E. P.: Relative Value of Surgery and Roentgen Ray in Treatment of Hyperthyroidism, J. A. M. A. **80**:820 (March 24) 1923.

Clute.[21] Of their 24 cases of thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter, there were persistences in 19 and recurrences in 5. In the recurrent cases there were no symptoms for an average of two years after operation, but in one case they were absent for only a few months. Richter [7] remarked on the slight incidence of true recurrences. This scarcity of recurrences enables us to make the general statement that if after subtotal thyroidectomy for exophthalmic goiter the basal metabolism drops to normal and remains there when iodine is not being administered, for as long as two months,[22] a cure can almost be assured.

It is also of prognostic interest that a basal metabolic rate of plus 15 per cent or higher during the administration of iodine for from ten to fourteen days after operation, usually means that the disease has not been abolished. On the other hand, if the basal metabolism is normal for from ten to fourteen days after operation and iodine is being administered, a cure can by no means be assured. While the data are not extensive enough for one to draw definite conclusions, it appears that similar prognoses may be made regarding patients who do not receive iodine during the immediate preoperative and postoperative periods. However, if the basal metabolic rate is normal for from ten to fourteen days after operation in these patients it can usually be assumed that the disease has disappeared. Segall and Means,[23] and Richardson and Means [24] observed that in cases in which the patients were apparently cured by subtotal thyroidectomy before the days of the use of iodine the basal metabolism was usually normal within two weeks after operation.

CHRONICITY

The chronicity of postoperative thyrotoxicosis is of interest. Good examples of this are given in charts 5, 8 and 9. In the cases of persistence in which measurement was possible, the shortest duration of the disease in a patient who received no other treatment after operation except iodine was one and one-fourth years. In two thirds of the

21. Lahey, F. H., and Clute, H. M.: Persistent and Recurrent Hyperthyroidism, Ann. Surg. **83**:199, 1926.

22. This figure is made to err on the side of conservatism, in order to allow ample time for the effect of medication with iodine to wear off. An interval of one month would be sufficient for practically all cases.

23. Segall, H. N., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, Arch. Surg. **8**:176 (July) 1924.

24. Richardson, E. P., and Means, J. H.: Results of Surgery and of Surgery Combined with Roentgen Ray Treatment in Exophthalmic Goiter, Arch. Surg. **2**:237 (Sept.) 1924. Means, J. H., and Richardson, E. P.: Diseases of the Thyroid, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 208.

cases of persistence the disease lasted for at least a year; in one quarter of the cases it persisted for at least from two to six years, without indication that it was coming to an end. Incidentally, one patient who was first operated on for exophthalmic goiter in the Massachusetts General Hospital in 1909 still had the disease in moderately severe form in 1927 in spite of two more thyroidectomies; that is, in this case there was a persistence of at least nineteen years. In one of the cases of recurrence in this series (chart 3), the thyrotoxicosis lasted a minimum of one year and possibly for from three to four years. We had great difficulty in finding a case in which the disease ended after a few months. The case of one patient in whom it apparently did so is not included in this study, because we were somewhat uncertain as to whether or not she was thyrotoxic after operation. The gain in weight and the diminution in nervousness, however, when the basal metabolic rate of this patient dropped to normal seven months after operation make it appear probable that she had thyrotoxicosis during the immediate postoperative period. Clute [25] gave the duration of persistences at the Lahey Clinic as from three months to fourteen years. It would be of interest to know what effect, if any, subtotal thyroidectomy has on the duration of the disease in these cases.

Not only was postoperative thyrotoxicosis a chronic condition in our cases of persistence, but it rapidly reached a steady state, and remissions were not noted, except those associated with the administration of iodine or the ending of the disease, and relapses were not observed, except those associated with the omission of iodine. This, together with the scarcity of true recurrences, leads us to wonder whether the remissions and relapses in the disease are not overemphasized. Either this is true, or else the thyrotoxicosis is different in this respect after operation than before.

CAUSE, INCLUDING RELATION TO EXTENT OF THYROIDECTOMY

Several observers [26] agreed that one of the chief causes of thyrotoxicosis following subtotal thyroidectomy is the removal of too little thyroid tissue. In our series, this idea is supported by the fact that the surgeons who did the most complete thyroidectomies had definitely the

25. Clute, H. M.: Hyperthyroidism Persisting after Thyroidectomy: The Necessity for Postoperative Examinations in Toxic Goiters, S. Clin. North America **6**:691, 1926.

26. Else, J. E.: Prevention of Recurrent Goiter, S. Clin. North America **8**:1375, 1928. Gilman, P. K., and Kay, W. E.: Certain Advantages of Total Thyroidectomy in Selected Cases of Thyrotoxicosis of the Exophthalmic Type, Am. J. M. Sc. **175**:350, 1928. Lahey, F. H.: Review of Another Year's Work with Thyroid Disease, Boston M. & S. J. **190**:153, 1924. Elliott (footnote 8). Frazier and Mosser (footnote 10). Smith, Clute and Strieder (footnote 14). Waits (footnote 17). Clute (footnote 25).

smallest percentage of persistences; by the fact that the thyrotoxicosis represented primarily a persistence of the disease rather than a recurrence, and by the fact that there was no outstanding difference before operation between the patients who were thyrotoxic following operation and those who were not. It may have been because operation was performed by the less experienced surgeons in a much larger percentage of cases in 1928 than in preceding years that the incidence was so high in that year. Else [27] reported that he has observed a considerable increase in the number of "recurrences" since "unspecialized general surgeons" have been doing goiter operations. Levin [28] was under the impression that "recurrences" are more common in goitrous areas, in which presumably lack of iodine is a factor.

The cause of true recurrences is not so easily explained. Just as the cause of the initial appearance of the disease is unknown so is it at present unknown why the condition should again become active after a period of quiescence. Pemberton [11] stated the belief that infections, overwork, worry, fright, shock, pregnancy and operations are important factors in recurrences. As stated previously, postoperative thyrotoxicosis, in general, seemed to be associated with the presence of a considerable amount of palpable thyroid tissue, and the amount was usually large in those patients who showed only temporary improvement during the administration of iodine. In the cases in which the disease finally disappeared and in which data were available (in case 1812, chart 3; in case 3913, chart 4, and in cases 2031, 2759 and 3961), the palpable tissue decreased markedly, usually to the point of becoming nonpalpable. Thus there was a rough parallelism between the amount of palpable tissue and the degree of thyrotoxicosis. It is of some diagnostic interest that, following subtotal thyroidectomy, an amount of thyroid tissue sufficient to be palpated with ease usually means that thyrotoxicosis is present. There are, of course, cases of severe postoperative thyrotoxicosis occasionally encountered in which no thyroid tissue can be palpated. Phemister [29] had a patient in whom two nodules, which at operation were only the size of a pea, were causing a severe persistence with a rate of basal metabolism of plus 50 per cent. Lahey and Clute,[21] however, remarked that they had repeatedly been surprised at the size of the remnant at operation when none could be palpated beforehand, probably because it was situated on the posterior lateral aspects of the trachea.

27. Else (footnote 26, first reference).

28. Levin, S.: Comparative Study of 100 Subtotal Thyroidectomies from a Single Goiter Zone, J. Michigan M. Soc. **24**:527, 1925.

29. Phemister, in Miller, J. L.: Thyrotoxicosis from the Internist's Standpoint, Am. J. M. Sc. **177**:98, 1929.

Persistence in Spite of Extensive Thyroidectomy.—In several instances in our series, even in cases of persistence, it was observed that the tissue palpable was not simply that left at operation, but was at least in part a new growth. Because of the marked propensity of the thyroid remnant to regenerate in some cases, it is probably impossible at present to prevent a certain amount of postoperative thyrotoxicosis, no matter how complete the thyroidectomy and by whom it is performed. This is illustrated by certain cases in the present study.

CASE 5581.—Miss V. G. (chart 7) had a right hemithyroidectomy for exophthalmic goiter March 16, 1928, about seven eighths of the lobe being removed. The administration of a compound solution of iodine was continued after operation, and by May 16, the basal metabolic rate was higher than it was during the administration of iodine just before operation; and not only were the left lobe and isthmus of the thyroid much larger, but there was also palpable tissue in the right lobe equal to at least three or four times the amount left at operation. On June 1, a second operation was performed, at which the isthmus and all except about 4 Gm. of the left lobe were removed. Following the operation the metabolism remained slightly elevated in spite of the administration of iodine, and by October 17, a mass of tissue the size of a walnut was palpable in the right lobe, and one the size of a cherry in the left lobe. About a month later the palpable tissue had increased still further in size. Omission of iodine on Feb. 25, 1929, was followed within a month by a rise in basal metabolic rate from plus 15 per cent to plus 38 per cent, and a return of all the signs and symptoms of thyrotoxicosis.

CASE 1915.—Mr. F. H. L., in whose case the data are recorded in chart 5, was apparently continuously thyrotoxic for a period of from twelve to sixteen years, in spite of two hemithyroidectomies and a subsequent subtotal thyroidectomy done by one of the two surgeons who do the most complete thyroidectomies and have the smallest incidence of postoperative thyrotoxicosis. The rate of basal metabolism at the time of the last observation was only slightly lower than before the first operation. Although recurrent tissue in the isthmus and in both lobes was removed in the subtotal thyroidectomy, there was a nodule in the left lobe of at least the size of a cherry at the time of the last observation.

CASE 6397.—The situation was somewhat similar in the case of Miss K. M. R., the data in whose case are given in chart 10. The thyrotoxicosis which had been present for about four years before admission to the hospital, and in which nervousness was perhaps the most outstanding feature, was only partially relieved by two subtotal thyroidectomies, although tetany followed the second. Within seven weeks after the first operation the basal metabolism was as high as it had been initially, and three weeks later, when induration had disappeared from the scar, a mass of thyroid tissue the size of a walnut was palpable on each side of the trachea. In another month and a half, this mass had doubled in size. There appeared to be a considerable amount of thyroid tissue palpable following the second operation, but there was still too much induration about the scar for us to be sure of this. (The short periods of normal metabolism following the operations during the administration of iodine probably do not represent true disappearances of the disease, but merely marked reductions in its intensity until thyroid tissue had time to regenerate.)

In such patients the disease must differ in some fundamental respect from that in the large number of cases in which it apparently comes to an end following one extensive thyroidectomy. If the reason for the new growth of thyroid tissue is merely that the cause of the disease is still active, it is remarkable that in at least 80 per cent of the cases of exophthalmic goiter the condition appears to be permanently cured by one subtotal thyroidectomy. It is difficult to understand why the cause of the disease should apparently suddenly cease to act altogether in such a large proportion of cases. The result one would expect would be a persistence of the disease in a mild form, according to the proportion of the gland left in situ. It is possible, of course, that the gland, having already shown marked hyperplasia, is unable to respond thus still further to any but strong stimuli. In this connection it is of interest that all of the cases like the three already mentioned, in which the disease showed such a striking tendency to persist, were in patients who originally had the disease in severe form, and in whom the accompanying emotional instability was marked. Certainly some powerful stimulus must be stimulating the thyroid in such a patient as in case 5581 (chart 7) in order to cause the lobe left in situ to double in size and the remnant on the hemithyroidectomized side to show marked proliferation.

The regrowth of thyroid tissue, although it may be marked, rarely reaches the size of the gland before surgical measures are used. This is probably the reason that the patients, although toxic, show improvement—there is merely a smaller mass of tissue to secrete the toxic agent, which is thus presumably secreted in smaller amount.

THE RESPONSE TO IODINE

On the whole, the response to iodine was much more satisfactory in this group than in an unselected group of patients with exophthalmic goiter who had not been otherwise treated. As previously demonstrated, in many cases the basal metabolic rate could be held at a constant level and the symptoms of thyrotoxicosis more or less completely controlled as long as iodine was continuously administered. These good results with iodine are possibly to be attributed to the decrease in the severity of the disease caused by operation, for, as we have shown,[30] there is a group of mild cases in which it is possible to treat the patients satisfactorily by iodine alone, whereas moderately severe and severe cases rarely show more than temporary improvement. It seems that similarly many of these cases of postoperative thyrotoxicosis can be carried along

30. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med. **45**:481 (April) 1930.

for years on such a regimen and, at least in some instances, until the disease disappears (case 1812, chart 3; case 3913, chart 4, and case 2031). Read [31] and Jackson [32] reported satisfactory control of postoperative thyrotoxicosis by the use of iodine. At the Lahey Clinic, Smith, Clute and Strieder [14] reported that of 7 cases of persistence only 2 were uncontrolled by iodine. In reports from the same clinic by Clute [25] and Lahey and Clute,[21] however, it was stated that in several of the cases in which there was thyrotoxicosis following operation iodine was administered for a year or more, usually with temporary, but in no case permanent, improvement. In our series it was more common for the rate of basal metabolism to remain depressed at a more or less constant level as long as iodine was continuously administered, than for the depression to be only temporary. It is a matter of considerable interest that while the metabolism could be held at a fairly constant level by the administration of iodine in so many cases, there were only 6 cases in which it was constantly held below plus 10 per cent.

But for the use of iodine postoperatively, more of these patients would have come to second operation; incidentally this is a different matter from the number of patients having persistence of the disease. The fact that the basal metabolism can be held at a constant level by iodine, however, does not necessarily mean that the result is entirely satisfactory. The best results would probably be secured by reoperating in all cases in which the basal metabolism cannot be held indefinitely at plus 15 per cent or lower by the administration of iodine.[33] While in some patients in whom it is held at this or a slightly higher level the thyrotoxicosis is held fairly well in check, nevertheless a few signs and symptoms may be detected by careful observation. There is reason to suppose that the continued maintenance of a basal metabolic rate of from plus 15 to 25 per cent for several years may result in damage to the circulatory and other systems. For example, in a girl, aged 16 (lab. no. 5040, not in this series), the slight load imposed on a damaged heart (rheumatic) by mild postoperative thyrotoxicosis (with a metabolism of plus 25 to 30 per cent in spite of medication with iodine) caused symptoms of mild cardiac failure. When this load was removed by a second operation (subtotal) and the basal metabolism was restored to normal, these symptoms disappeared and the patient's heart was able to meet the demands of ordinary routine. In a patient whose heart

31. Read, J. M.: The Use of Iodine in Exophthalmic Goiter, Endocrinology **8**:746, 1924.

32. Jackson, A. S.: Goiter and Other Diseases of the Thyroid Gland, New York, Paul B. Hoeber, Inc., 1926.

33. This will automatically include most patients with a large amount of palpable thyroid tissue. Treatment with roentgen rays is, on the whole, a rather unsatisfactory method.

was not diseased, similar cardiac symptoms would rarely result from the same degree of thyrotoxicosis. Nevertheless, it seems reasonable to suppose that the extra load thus thrown on the heart probably causes some damage which, although not obvious at the moment, may show up in the course of time.

Else [34] and Levin [28] claimed that the postoperative administration of iodine prevents the regrowth of thyroid tissue after subtotal thyroidectomy for exophthalmic goiter; and Richter [7] that it at least tends to lessen the number of recurrences. Marine and Lenhart [35] showed that the administration of iodine will prevent compensatory hyperplasia following partial removal of the thyroid in normal animals or in those with colloid goiter. This is a different matter, however, from preventing hyperplasia in the gland in exophthalmic goiter. On the other hand, Miller,[36] Clute [25] and Sloan [37] claimed that the postoperative administration of iodine does not prevent the regeneration of tissue or recurrence in exophthalmic goiter glands after thyroidectomy. Our observations appear to support this hypothesis. In other words, iodine does not seem to affect the cause of the disease. It follows that from the standpoint of prevention of postoperative thyrotoxicosis it is immaterial for how long the administration of iodine is continued after operation.

RELATION OF EXTENT OF THYROIDECTOMY TO MYXEDEMA, TETANY AND PARALYSIS OF THE RECURRENT LARYNGEAL NERVE

The large percentage of persistences in our series may not be an unmixed evil. We (W. O. T. and P. K. T.) [38] showed that true postoperative myxedema (not merely low basal metabolism) is at present a comparatively rare phenomenon at the Massachusetts General Hospital (about 1 per cent of the cases in which operation was done). Richardson [39] believed that "the removal of too much thyroid tissue is very improbable if the operation is carried out with due regard for the safety of the parathyroid glands and recurrent nerves." In certain other

34. Else, J. E.: Regeneration of the Thyroid Gland and the Prevention of Recurrent Goiters, J. A. M. A. **89**:2153 (Dec. 24) 1927.

35. Marine, D., and Lenhart, C. H.: Relation of Iodine to the Structure of Human Thyroids: Relation of Iodine and Histologic Structure to Diseases in General; to Exophthalmic Goiter; to Cretinism and Myxedema, Arch. Int. Med. **4**:440 (Nov.) 1909.

36. Miller, J. L.: Thyrotoxicosis from the Internist's Standpoint, Am. J. M. Sc. **177**:98, 1929.

37. Sloan, H. G., in discussion of article by Else (footnote 34).

38. Thompson, W. O., and Thompson, P. K.: Temporary and Permanent Myxedema Following Treated and Untreated Thyrotoxicosis, J. Clin. Investigation **6**:347, 1928.

39. Richardson, E. P.: Personal communication to the authors.

clinics, however, the incidence of myxedema is said to have increased as the thyroidectomies have become more extensive. For example, according to Richter,[9] thyroidectomies sufficiently extensive to cause a high percentage of cures "will result in a high incidence of temporary hypothyroidism." Gilman and Kay [26] reported that 19 of 20 patients who underwent a so-called total thyroidectomy required the administration of desiccated thyroid following operation (the other patient died), but the reasons for assuming that an underfunction of the thyroid was present were not stated in most instances. In 2 other patients in their series who required no desiccated thyroid following operation, a nodule of tissue 1 by 1 cm. was left in by request. Smith, Clute and Strieder [14] said that the incidence of postoperative myxedema has increased in the last three years at the Lahey Clinic, in association with a marked increase in the amount of tissue removed at operation and the use of iodine postoperatively. Richter,[9] indeed, regarded hypothyroidism as the goal of subtotal thyroidectomy. We are not convinced that an underfunction of this important organ is any more desirable than a mild overfunction.

Of course, care must be taken to distinguish between a low rate of basal metabolism caused by an underfunction of the thyroid and one associated with other conditions.[40] If it be true, however, that extensive thyroidectomies result in a high incidence of myxedema, then in our opinion the goal of surgery is to leave in an amount of tissue large enough to prevent the development of myxedema and small enough to prevent a persistence of the disease. Much can undoubtedly be done in this direction, but the goal will be hard to achieve because of the variation among patients in the amount of this tissue and the technical difficulties of leaving in only a certain amount at operation. These obstacles perhaps serve to emphasize that surgical intervention, while at present the best method of treatment for exophthalmic goiter, is in reality a rather crude one.

The incidence of tetany, at present a much more serious sequel than the persistence of exophthalmic goiter in a mild form, is low, being only about 1 per cent. Figures showing the incidence of tetany following operations for goiter at other clinics are not available. Elliott [41] and

40. Thompson, W. O.; Thompson, P. K., et al.: Low Basal Metabolism Following Thyrotoxicosis: I. Temporary Type without Myxedema, with Special Reference to the Rôle of Iodine Therapy, J. Clin. Investigation **5**:441, 1928; Low Basal Metabolism Following Thyrotoxicosis: II. Permanent Type without Myxedema, ibid. **5**:471, 1928; Significance of Low Basal Metabolism Following Thyrotoxicosis, Am. J. Surg. **7**:48, 1929. Thurmon, F. M., and Thompson, W. O.: Low Basal Metabolism without Myxedema, Arch. Int. Med. **46**:879 (Nov.) 1930.

41. Elliott, C. A.: Results of Thyroidectomy for Hyperthyroidism as Indicated by Examination a Year or More Following Operation, Tr. A. Am. Physicians **41**:93, 1926.

Boothby [42] were under the impression that postoperative tetany has increased since subtotal thyroidectomies have become more extensive. There were 3 patients with postoperative tetany among the 266 patients operated on during the six year period included in our study. Two cases occurred in patients who were not thyrotoxic after operation. One of these patients died shortly after operation. In the other, the signs and symptoms of tetany practically cleared up, although the concentration of calcium in the serum remained rather low. In the third patient, the tetany was still marked up to the time of writing. The first 2 patients were among those operated on by a surgeon who had one of the smallest number of persistences. The third patient (no. 6397, chart 10 in this study) was among those operated on by another surgeon who had a high percentage of persistences, which he was much interested in reducing. On this patient he performed two subtotal thyroidectomies, and at the second operation he made the removal of the remaining thyroid tissue much more thorough than was his usual practice. Nevertheless, he took care to identify and to leave two parathyroids, so that tetany was apparently an unfortunate coincidence.

Paralysis of the recurrent laryngeal nerve has not been common at this hospital and has usually been transient in its effect on phonation. It may occur following incomplete thyroidectomy.

In the hands of the average surgeon, more radical thyroidectomies would probably mean more tetany, more recurrent paralysis of the laryngeal nerve and more laryngeal edema. It is our impression, however, that there is about as little danger of these complications when an experienced surgeon does an extensive thyroidectomy as when an inexperienced one does a much less extensive operation.

SUMMARY

Of 190 cases of exophthalmic goiter in which the patients underwent subtotal thyroidectomy during the years 1923 to 1928 at the Massachusetts General Hospital and which were followed for from three months to nearly six years after operation with frequent physical examinations and tests of basal metabolism, 37, or 19.5 per cent, showed definite clinical evidence of postoperative thyrotoxicosis with basal metabolic rates ranging from plus 19 to plus 63 per cent without medication.

In only 2 instances was there evidence that it was a true recurrence rather than a persistence of the disease. In 3 cases, however, regeneration of thyroid tissue was observed in association with a persistence. This condition was sometimes noted in spite of the administration of iodine and repeated subtotal thyroidectomies.

42. Boothby, W. M., in discussion of article by Elliott (footnote 41).

The postoperative thyrotoxicosis lasted from about two to four years in the 3 cases in which it finally disappeared without further surgical measures or roentgen treatment. It lasted for at least one year in 19 others and at least from four to six years in 4 others.

The degree of thyrotoxicosis was usually not severe; with a single exception, it was less than before operation. All of the patients resumed their customary occupation, although under a definite handicap in the instances in which the disease persisted in moderately severe and in severe form.

In 18 cases the basal metabolism could be held at a constant level for from months to years by the prolonged administration of iodine. In 10 cases in which iodine was ineffective, or eventually became so, or in which it did not abolish the thyrotoxicosis completely enough, reoperation was recommended. In 7 cases roentgen therapy was tried, with fair results in 5 instances.

From a preoperative standpoint, there was no definite distinguishing mark between those patients who had thyrotoxicosis following operation and those who did not.

There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of thyrotoxicosis.

The surgeons who did the most radical thyroidectomies (synonymous in general with those who had the most experience) had definitely a smaller percentage of cases of postoperative thyrotoxicosis than did the surgeons who had less experience and who usually did less extensive thyroidectomies.

In the cases of persistence of the disease, we noted no relapses except those caused by the omission of iodine, and no remissions except those caused by its administration and the disappearance of the disease.

CONCLUSIONS

Thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter appears in most cases to be caused by the removal of too little thyroid tissue at the time of operation.

A reduction in the incidence of postoperative thyrotoxicosis without an increase in the incidence of myxedema, tetany or paralysis of the recurrent laryngeal nerve, however, will occur only when more radical thyroidectomies are performed by surgeons specially trained to do this type of work.

Owing to the marked propensity of the remnant of thyroid tissue to regenerate shortly after operation in some cases, it is probably impossible at present to prevent a certain amount of persistence of the disease no matter how complete the thyroidectomy (exclusive of complete extirpation) and by whom it is performed.

If the basal metabolism is plus 15 per cent or higher for from ten to fourteen days after a subtotal thyroidectomy for exophthalmic goiter and if the patient is receiving iodine during this period, it is probable that the disease will persist. On the other hand, a normal metabolic rate under these conditions does not mean that the disease has been abolished.

If, following subtotal thyroidectomy, a patient has a normal metabolism for as long as two months during a period in which he is not receiving iodine, the danger of his having the disease again is slight.

Thyrotoxicosis is almost always present if following subtotal thyroidectomy for exophthalmic goiter there is an amount of thyroid tissue sufficient to be easily palpable.

It is probably desirable to reoperate on all patients in whom the basal metabolic rate cannot be held at or near the standard normal level by the continuous administration of iodine until the disease disappears.

The favorable response to prolonged medication with iodine noted in many patients after subtotal thyroidectomy is similar to the favorable response noted in many patients who have the disease in mild form but who have not been otherwise treated, and may be the result of reduction in the severity of the disease following operation.

The postoperative administration of iodine does not prevent the regeneration of thyroid tissue or a persistence of thyrotoxicosis.

The marked chronicity of the thyrotoxicosis following subtotal thyroidectomy suggests that in such instances the disease may last as long as it would have if no operation had been performed.

THE NEUTRAL RED TEST IN PERNICIOUS ANEMIA *

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During the past year we were able to demonstrate the presence of injected neutral red in the gastric extractions of three patients who had pernicious anemia. These determinations prompted us to make this report.

The use of neutral red has been advocated in the study of the gastric secretory function. Fuld [1] discovered that neutral red would appear in a Pavlov pouch after the dye was placed in the large stomach. Several years later, Finkelstein [2] found that it was practically the only dyestuff eliminated in appreciable quantities in the Pavlov pouches of dogs after intramuscular administration. One year later, Glaessner and Wittgenstein [3] applied this fact clinically.

Davidson, Willcox and Haagensen [4] concluded that neutral red was excreted in achylia accompanying every condition except pernicious anemia. In their studies, they investigated eight cases of pernicious anemia, and did not recover neutral red in the gastric extractions after two hours. Their statement that the absence of the dye in pernicious anemia, in contrast to its excretion even in small amounts in carcinoma with anacidity, and secondary anemia with anacidity, is of definite practical value.

In a recent communication, Winkelstein and Marcus [5] stated that true achlorhydria occurs in a variety of conditions, and that the failure of neutral red to appear is linked with the absence of the acid and is not

* Submitted for publication, April 21, 1930.

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1. Fuld, E.: München. med. Wchnschr. **43**:908, 1908.

2. Finkelstein, R.: Arch. f. Verdauungskr. **30**:299, 1923.

3. Glaessner, K., and Wittgenstein, H.: Klin. Wchnschr. **2**:1650 (Aug. 27) 1923.

4. Davidson, P. B.; Willcox, E., and Haagensen, C. D.: Gastric Excretion of Neutral Red, J. A. M. A. **85**:794 (Sept. 12) 1925.

5. Winkelstein, A., and Marcus, J.: Excretion of Neutral Red in the Stomach in Achylia Gastrica, J. A. M. A. **92**:1238 (April 13) 1929.

determined by the type of disease present. They were impressed with the fact that a single and, occasionally, a repeated Rehfuss fractional test meal is not enough to establish the diagnosis of true achlorhydria or achylia gastrica. In the group of false diagnoses of achylia a small amount of acid is produced and is neutralized by duodenal regurgitation or perhaps by the protein from a gastric carcinoma or other neoplasm that is breaking down. Winkelstein and Marcus stated that they did not encounter one case of pernicious anemia in which neutral red was excreted.

METHOD OF DETECTION OF NEUTRAL RED IN EXTRACTED SPECIMENS

A Rehfuss tube is introduced into the "fasting stomach," and the stomach is washed with water until the contents return water clear. Two cubic centimeters of a 2 per cent solution of neutral red (40 mg.) is injected intramuscularly into the gluteal region. The stomach is then aspirated every fifteen minutes for two hours. Each specimen is kept in a separate test tube. In cases in which there is very little or no gastric secretion, a quantity of water, 15 or 20 cc., is introduced into the stomach through the tube and aspirated at the end of the fifteen minute periods.

The gastric contents are then treated in the following manner: To 15 or 20 cc. of the contents of the stomach, approximately 2 Gm. of tribasic lead acetate is added, and the tube shaken. If the contents seem to contain a large quantity of bile, about 1 Gm. of purified animal charcoal is also added. This is filtered through filter paper, and within a few minutes sufficient filtrate is obtained to fill a small test tube. When smaller quantities of the contents of the stomach are used, proportionate amounts of the lead acetate and charcoal are employed. A few drops of glacial acetic acid are added to the filtrate while it is viewed against a pure white background (such as white paper) and while a control tube with plain water is held next to it. When neutral red is present the solution will begin to assume a pinkish color within a few seconds. The depth of the color is proportional to the concentration of the dye. We have not attempted to determine the quantitative output of the neutral red.

REPORT OF CASES

Case 1.—C. B., a woman, aged 38 years, six weeks prior to admission to the hospital began to complain of increasing weakness, discoloration of the skin and a tingling sensation in the fingers. The patient showed an icteric tint to conjunctiva, marked atrophic glossitis, a hard spleen, the absence of knee jerks, diminished deep reflexes, blurred disks and retinal hemorrhages.

The results of a roentgen examination of the gastro-intestinal tract were negative. The gastric extraction on admission to the hospital showed: free acidity, 0 0 0 0 0 0; total acidity, 5 0 10 12 10 5. The guaiac reaction was negative. Gastric extraction two weeks later showed: free acidity, 0 0 0 0 0 0; and total acidity, 10 12 38 50 20 10. The guaiac reaction and the test for lactic acid were negative. The blood count on admission showed: red blood cells, 1,596,000 per cmm.; white blood cells, 2,400 per cmm., and hemoglobin (Dare), 28 per cent. The color index was 0.9. The differential count showed: polymorphonuclears,

57 per cent; small lymphocytes, 38 per cent; eosinophils, 2 per cent; metamyelocytes, 2 per cent, and myelocytes, 1 per cent.

Anisocytosis and macrocytosis were moderate. There was marked poikilocytosis and slight polychromasia. The hemolysis test started at 0.42 per cent sodium chloride, and finished at 0.34 per cent.

CASE 2.—G. W., a woman, aged 28, had for five months complained of weakness, a sore tongue and increasing pallor. Examination showed a lemon yellow

TABLE 1.—*Results of Testing the Contents of the Stomach to Determine the Presence of Neutral Red*

Specimen	Acid	Dye	Time
1	0	0	15 min.
2	0	0	30 min.
3	0	0	45 min.
4	0	0	1 hr.
5	0	0	1¼ hr.
6	0	0	1½ hr.
7	0	Present	1¾ hr.
8	0	Present	2 hr.

Bilirubin: direct, negative; indirect, 2 units
Icteric index, 15

TABLE 2.—*Test for Neutral Red*

Specimen	Free Acid	Total Acidity	Dye	Time
1	0	6	0	30 min.
2	0	8	0	45 min.
3	0	6	Present	1 hr.
4	0	10	Present	1½ hr.
5	0	6	0	2 hr.

TABLE 3.—*Test for Neutral Red*

Specimen	Free Acid	Dye	Time
1	0	0	20 min.
2	0	0	40 min.
3	0	Present	1 hr.
4	0	0	1½ hr.
5	0	Present	2 hr.

skin, atrophic glossitis and a palpable spleen. The results of a roentgen examination of the gastro-intestinal tract were negative. Gastric analysis, including a fractional study with histamine as the stimulant, made on four occasions, failed to disclose any free hydrochloric acid. The blood count was: red blood cells, 2,800,000 per cmm.; white blood cells, 6,600 per cmm.; hemoglobin (Dare), 45 per cent. The color index was 0.9. The differential count showed: polymorphonuclears, 42 per cent; lymphocytes, 56 per cent, and eosinophils, 2 per cent.

There was marked anisocytosis, macrocytosis, polychromasia and poikilocytosis, and slight microcytosis.

CASE 3.—M. W., a woman, aged 51 years, for the past few months had complained of numbness, weakness of the lower extremities and progressive anemia.

Examination showed marked pallor, atrophy of the marginal papillae of the tongue, presence of the knee jerks, the loss of vibratory sensation and a diminished tactile sensation in the lower extremities. The Babinski sign was present on the patient's right side. The results of the roentgen examination of the gastrointestinal tract were negative. Repeated gastric analyses showed no free hydrochloric acid (one study was made with histamine as the gastric stimulant).

The blood count showed: red blood cells, 2,140,000; white blood cells, 3,800, and hemoglobin (Dare), 50 per cent. The color index was 1.1. The differential count showed: platelets, 170,000; polymorphonuclear neutrophils, 63 per cent; polymorphonuclear eosinophils, 1 per cent, and small lymphocytes, 36 per cent.

Macrocytosis and polychromasia were moderate; microcytosis was slight. There was a reticulation of 0.5 per cent.

COMMENT

We are not able to state whether the neutral red recovered in the gastric extractions of these patients was actually secreted by the gastric glands or whether it was regurgitated from the duodenum into the stomach. Experimental work in herbivorous and omnivorous animals by Piersol, Bockus and Banks [6] definitely showed that neutral red is excreted to a considerable degree in the bile as well as in the intestinal glands from the duodenum to the ileum. The possibility that the dye might be swept back into the stomach by duodenal regurgitation, particularly in cases of achylia in which the pylorus is frequently open, should receive serious consideration.

The presence or absence of bile in the extracted specimens, as shown by Medes and Wright,[7] does not determine whether or not there has been duodenal regurgitation. They found in their studies evidences of duodenal regurgitation even in the absence of bile in the extracted specimens. In brief, these authors showed that bile is regurgitated rarely without trypsin, and that trypsin is regurgitated much more frequently without bile.

The possibility that the neutral red recovered in these cases was of gastric origin cannot be excluded. One cannot depend entirely on the appearance and color of the extracted specimen to determine whether or not neutral red is present. Bile pigment, if present, must be removed, and in any event the specimen must be acidified in order to establish definitely the presence or absence of the dye.

We are now engaged in the study of the biliary excretion of neutral red in man by injecting it at variable times prior to cholecystectomy.

SUMMARY

1. Three cases have been reported of patients with pernicious anemia in whom injected neutral red was recovered in the gastric extractions.

6. Piersol, G.; Bockus, H., and Banks, J.: Am. J. M. Sc. **170**:405, 1925.

7. Medes, G., and Wright, C. B.: J. Clin. Investigation **6**:403 (Dec.) 1929.

2. Previous investigators have emphasized the diagnostic value of the neutral red test in pernicious anemia.

3. Investigators have never before been able to recover neutral red in the gastric specimens in true pernicious anemia.

4. The value of the test for neutral red is always questionable, because the presence of the dye in the stomach may be accounted for by regurgitation of the duodenal content.

5. A simple and rapid method for the detection of neutral red in the gastric content is described.

6. The presence of neutral red in the gastric extractions does not in itself exclude the diagnosis of pernicious anemia.

THE DIAGNOSTIC VALUE OF THE SUGAR TOLERANCE CURVE IN ENDOCRINOPATHIES *

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Since Hofmeister (1888) first reported mellituria in dogs following the administration of dextrose, and Jacobson (1913) proposed a series of blood sugar determinations, as tests offering certain aids in the diagnoses of diseased states, particularly the endocrinopathies, there has been a regrettable confusion in the prolific literature pertaining to the sugar tolerance test. The work of the earlier investigators in general may be disregarded, because the methods were inexact, and the results necessarily unreliable.

With certain minor variations, the test consists in the administration of a standard amount of dextrose (100 Gm.) and the estimation of the sugar in the blood and urine at intervals thereafter. The proponents of this test base their diagnostic interpretation on the height attained by the curve, the rapidity of its return toward normal and the level of the blood sugar three hours after the administration of dextrose as compared with its level at the beginning of the test.

In order to reevaluate this test, I have analyzed over 300 sugar tolerance curves made in the Jewish Hospital in the last three years. During this period the same technician continuously employed the same method for determining the blood sugar (Shaffer-Hartmann). The micro-technic requiring 0.2 cc. of capillary (arterial) blood, which is rapidly finding extensive favor, was used.

Of the curves analyzed, eighty-five were grouped according to the diagnosis in the following classification: "normal," hyperthyroid, hypothyroid, hypopituitary and a combination hypothyroid-hypopituitary type.

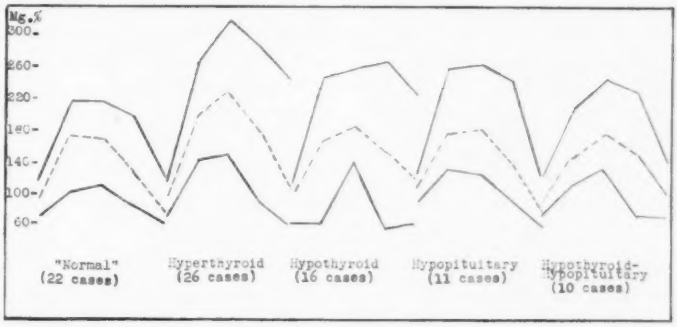
A glance at the chart, a graphic compilation of the observations in eighty-five cases, shows the lack of diagnostic significance that may be attached to the sugar tolerance curve because (*a*) the various cases of the same disease differ so widely in the blood sugar values, and (*b*) on the whole, the trend of the curves is not markedly different in the four conditions studied from that in the "normal" person.

Table 1 shows that the sugar tolerance curve repeated within a few days gives wide and inconstant variations.

* Submitted for publication, May 17, 1930.

* From the medical service of the Jewish Hospital, St. Louis.

In order to study at least one of the factors involved in this variability, I performed a test on four "normal" patients, giving dry dextrose without any fluid, and repeated the test within two or three days, this time giving the same amount of dextrose with a considerable quantity of water (from 800 to 1,200 cc.) during the course of the examination. The sugar was determined in both capillary (arterial) and venous blood in triplicate, employing Somogyi's (1929) technic. In table 2 are recorded the observations on capillary blood. In the first case the curves are almost identical, except at the one-half hour period, if the difference found in the sugar content during fasting is subtracted from the difference found during the other periods in the examination. However, in the other cases there is a striking variability amounting in the third case at the half-hour period to 41 mg. per hun-



Graphic reconstruction of a table (omitted because of its unwieldiness) showing maximum (upper straight line), average (broken line) and minimum (lower straight line) levels of eighty-five classified sugar tolerance curves. Note that the overlapping of the curves is such as to preclude almost entirely any diagnostic significance of any one sugar tolerance test.

dred cubic centimeters and in the fourth case to 68 mg. per hundred cubic centimeters at the one hour period. The average deviation, it is true, is only about 15 mg. per hundred cubic centimeters if the deviation during the fasting period is subtracted from that found during the other periods. However, it is obvious that little diagnostic significance can be attached to the test when the mere variation in fluid intake causes as much as 68 mg. per hundred cubic centimeters difference in the sugar value.

In table 3 are recorded the differences in venous sugar content after the administration of dry dextrose and after the administration of the same quantity of dextrose with a considerable amount of water (from 800 to 1,200 cc.). Throughout this table there are rather striking differences

TABLE 1.—*Variations in the Blood Sugar Tolerance Curves in the Same Patient When Routine Tests Were Made Within a Few Days*

Case	Number of Test	Before Administration of Dextrose	Diff.	½ Hour After Administration of Dextrose	Diff.	1 Hour After Administration of Dextrose	Diff.	2 Hours After Administration of Dextrose	Diff.	3 Hours After Administration of Dextrose	Diff.
		Mg. of True Sugar per 100 Cc. of Blood									
1	First	120		215		175		145		80	
	Second	115	+ 5	200	+15	180	— 5	160	—15	80	± 0
2	First	110		255		265		215		175	
	Second	70	+40	180	+75	200	+65	175	+40	145	+30
3	First	75		175		240		275		215	
	Second	100	—25	245	—70	325	—85	290	—15	160	+55
4	First	105		175		260		280		250	
	Second	100	+ 5	185	—10	250	+10	250	+30		
5	First	125		195		250		240		230	
	Second	125	± 0	200	— 5	195	+55	195	+45	195	—35
	Third	130	— 5	195	+ 5	205	—10	195	± 0	160	—35
Average deviation			13		30		40		24		26

TABLE 2.—*Variations in the Blood Sugar Tolerance Curves of the Capillary Blood with and without the Administration of Water*

Case	Fluids	Before Administration of Dextrose	Diff.	½ Hour After Administration of Dextrose	Diff.	1 Hour After Administration of Dextrose	Diff.	2 Hours After Administration of Dextrose	Diff.	3 Hours After Administration of Dextrose	Diff.
		Mg. of True Sugar per 100 Cc. of Blood									
1	Without	58		132		126		93		70	
	With	82	—24	126	+ 6	150	—24	116	—23	95	—25
2	Without	91		145		193		167		127	
	With	84	+ 7	142	+ 3	200	— 7	131	+36	106	+21
3	Without	79		217		195		149		54	
	With	84	— 5	176	+41	207	—12	121	+28	67	—13
4	Without	80		126		151		144		134	
	With	87	— 7	180	—54	218	—68	156	—12	84	+50
Average deviation			11		26		28		25		27

TABLE 3.—*Variations in the Blood Sugar Tolerance Curves of the Venous Blood with and without the Administration of Water*

Case	Fluids	Before Administration of Dextrose	Diff.	½ Hour After Administration of Dextrose	Diff.	1 Hour After Administration of Dextrose	Diff.	2 Hours After Administration of Dextrose	Diff.	3 Hours After Administration of Dextrose	Diff.
		Mg. of True Sugar per 100 Cc. of Blood									
1	Without	66		72		75		69		65	
	With	79	—13	98	—26	107	—32	77	— 8	60	+ 5
2	Without	89		142		182		135		117	
	With	84	+ 5	133	+ 9	174	+ 8	124	+11	78	+39
3	Without	78		190		184		127		54	
	With	90	—12	160	+30	172	+12	97	+30	52	+ 2
4	Without	76		107		142		139		118	
	With	77	— 1	171	—64	197	—55	154	—15	78	+40
Average deviation			8		32		27		16		22

in the sugar content. As in the other instance, there is no uniform deviation in the form of the curve occasioned by the quantity of water taken during the test. The differences here amount to from 30 mg. more to 64 mg. less per hundred cubic centimeters at the half-hour period and even at the three hour period from 2 to 40 mg. more per hundred cubic centimeters in the second test.

CONCLUSIONS

1. After a statistical analysis of eighty-five sugar tolerance tests done as a routine in the Jewish Hospital of St. Louis on a series of normal and endocrinopathic patients, I am unable to find any one curve which may be considered diagnostic of any of the conditions under consideration.

2. Statistical analysis of curves repeated within a few days of the first routine sugar tolerance test shows no uniformity in the results, thus precluding further a diagnostic interpretation of the curve obtained.

3. Careful determination of the capillary (arterial) and venous blood sugar after the administration of a standard dextrose meal with and without the ingestion of water shows no uniform deviation in the form of the curve. Such a critical analysis did show that the intake of fluid alone produced a tremendous but not a constant deviation in the curve.

4. For the reasons presented here, I feel that the sugar tolerance curve as we have used it as a routine up to this time yields no information of diagnostic value in the differentiation of normal and endocrinopathic conditions.

Metropolitan Building.

THE REFLEX INFLUENCE OF THE COLON, APPENDIX AND GALLBLADDER ON THE STOMACH *

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AND
GEORGE H. MILLER, M.D.
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The present investigation was suggested by the study of the gastric manifestations associated with an irritable colon.[1] The epigastric distress was demonstrated to be gastric in origin. It is intensified by an aggravation of the bowel symptoms, and may be induced by a distention of the colon. In the roentgen examination of the gastro-intestinal tract, a pyloric spasm was the most prominent observation. There was also frequently an increase in the peristaltic action of the stomach. These observations were not constant and varied in different persons, but they were more evident during periods of apparent increased tension in the colon. These observations suggested that an alteration in the tone, particularly in the pyloric region and in the peristaltic action, was responsible for the epigastric distress, and that the latter was induced by a stimulation from the colon.

Clinical and roentgen observations [2] have strongly supported the theory of a reflex stimulation of the stomach from the gallbladder and the appendix. Experimental investigations of the problem have been concerned chiefly with the study of the reflex connection between the colon and the stomach.

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* Submitted for publication, May 28, 1930.

* From the Department of Internal Medicine, State University of Iowa.

* Presented in part before the Society of Clinical Investigation at Atlantic City, May 6, 1929, and before the International Physiological Congress, Boston, Aug. 20, 1929.

1. Smith, Fred M.; Miller, G. H., and Fowler, W. M.: The Gastric Manifestations Associated with a Spastic Colon, J. A. M. A. **93**:1932 (Dec. 21) 1929.

2. Cole, L. G.: Physiology of the Pylorus, Pilleus Ventriculi and Duodenum, as Observed Roentgenographically, J. A. M. A. **61**:762 (Sept. 6) 1913; Relation of Lesions of the Small Intestine to Disorders of the Stomach and Cap, as Observed Roentgenologically, Am. J. M. Sc. **148**:92, 1914. Brown, H. G.: Diagnosis of Certain "Stomach Cases," South. M. J. **7**:617, 1914. Aaron, C. D.: Chronic Appendicitis, Pylorospasm and Duodenal Ulcer, J. A. M. A. **64**:1845 (May 29) 1915. Finney, J. M. T., and Friedenwald, J.: Pylorospasm in Adults: Its Medical and Surgical Treatment, Am. J. M. Sc. **162**:469, 1921.

Cannon [3] observed a delay in the emptying time of the stomach following an irritation of the colon. This observation stimulated others to adopt a similar method in the investigation of the reflex connection between the colon and the stomach. White,[4] in a correlated, clinical and experimental study, concluded that a delay in the emptying time of the stomach is an exception in lesions of the lower part of the bowel. In the experimental animals, the results of introducing a strong irritant into the cecum were variable. Intense irritation induced vomiting; a less intense irritant was followed either by a delay or an increase in the time in which the gastric contents were expelled, whereas moderate stimulation had no apparent effect. Monroe and Emory [5] recently reported experiments in which the emptying time of the stomach of the dog was studied before and after the introduction of turpentine into the colon. They concluded that an irritation confined to the colon had no appreciable effect on the pyloric mechanism and the gastric peristalsis from the standpoint of the ability of the stomach to discharge its contents, and suggested that "so-called" gastric symptoms associated with colitis do not originate in the stomach.

Hughson [6] was concerned primarily with the investigation of the relationship of the reflex pylorospasm to the diseases of the digestive organs, and studied the influence of the trauma incident to the various operative procedures on the abdominal viscera on the emptying time of the stomach. He noted that the traumatization of any abdominal viscus in the dog by surgical procedure prolonged the emptying time of the stomach approximately 67 per cent for a period of about two weeks, and that the speed of the contraction waves was increased. He advanced a hypothesis that a spasm of the pylorus resulting from disease either within or adjacent to the abdominal cavity is solely due to an irritation of the peritoneal surface.

Barber and Stewart [7] noted striking changes in the peristaltic activity of the stomach, and at times marked pylorospasm following trauma of the gallbladder, appendix and duodenum, which they regard as reflex phenomena.

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3. Cannon, W. B.: Mechanical Factor of Digestion, New York, Longmans Green & Company, 1911.

4. White, F. W.: Effect of Stimuli from Lower Bowel on the Rate of Emptying of the Stomach, Am. J. M. Sc. **156**:184, 1918.

5. Monroe, R. T., and Emory, E. S.: The Effect of Irritation of the Colon on the Emptying Time of the Stomach, Am. J. M. Sc. **177**:389, 1929.

6. Hughson, Walter: Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs, Arch. Surg. **11**:136 (July) 1925.

7. Barber, W. H., and Stewart, George D.: Further Observations on Reflex Gastric Hypermotility, Proc. Soc. Exper. Biol. & Med. **17**:155, 1919.

Pearcy and Van Liere [8] reported an immediate reduction in the tone of the stomach, cessation of contractions and an inhibition of the pyloric and cardiac sphincters of the dog following a distention of the esophagus, duodenum, jejunum or colon, by means of a balloon. They furthermore indicated that a distention of any portion of the gastrointestinal tract induced an inhibition of the remaining sections.

In the present investigation, the influence of the irritation of the colon, appendix and gallbladder by croton oil on the tone and peristaltic action of the stomach was studied. Dogs anesthetized with barbital were employed. The stomach and the proximal part of the colon were exposed by a midline incision. The ileum was ligated or sectioned at its junction with the cecum in order to limit the action of the irritant to the colon. A balloon was introduced into the pyloric portion of the stomach through the duodenum, and the peristaltic action recorded on a

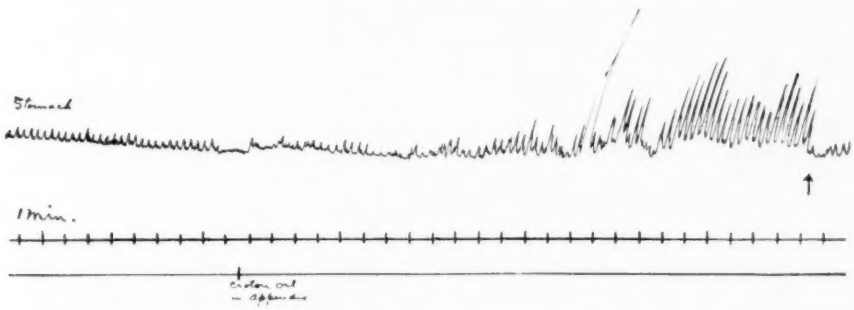

Chart 1.—Gastric activity after introducing croton oil into the first portion of the colon. It is noted that there was a striking increase in the peristaltic waves on distending the colon with air which subsided promptly on releasing the tension. The same characteristic response was again obtained which was later followed by an abrupt reduction in peristalsis subsequent to the administration of atropine.

kymograph. After a control period, a few drops of croton oil were introduced into the proximal colon by means of a syringe and small bore needle. Within a few minutes there was usually an increase in tone and a marked increase in the peristaltic action of the stomach which frequently became violent; occasionally, reverse waves were observed. This increased tone and peristaltic action of the stomach was intensified by distending the colon (chart 1). The effect of increasing and decreasing the tension of the colon following the application of the irritant were striking. The peristaltic waves were at once intensified by

8. Pearcy, J. F., and Van Liere, E. J.: Studies on the Visceral Nervous System: 1. Reflexes to the Stomach, Am. J. Physiol. **78**:64, 1926.

inflation and immediately subsided with the release in tension. This increase in tone and in the peristaltic action of the stomach, regardless of the intensity, was abolished by atropine. The reflex stimulation of the stomach from the irritation of the colon was observed, regardless of the depth of the barbital anesthesia. Comparable results were obtained when the irritation was limited to the appendix, and the response to atropine was identical (chart 2).

The reflex connection between the gallbladder and the stomach was studied in a similar manner. During the recording of the control period of the gastric activity, the gallbladder was aspirated. The remaining bile was removed by means of small cotton pledgets through an incision in the fundus of the gallbladder. The neck of the gallbladder was finally occluded by cotton to prevent the possibility of the croton oil

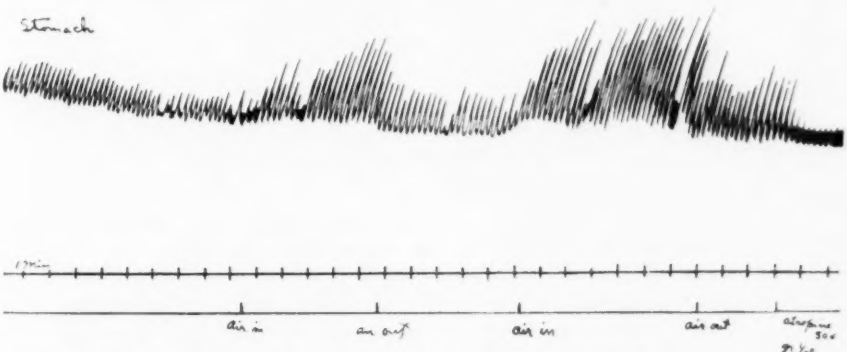

Chart 2.—Changes in the gastric activity following the introduction of croton oil into the appendix. During the increased gastric activity, the irritant in the appendix had induced circular areas of marked constriction. The results in this experiment were similar to those observed following the introduction of the irritant into the colon and gallbladder. In all instances there was a prompt response to the administration of atropine. The time of the administration of the atropine is indicated by the arrow.

passing down the duct. In some instances the common duct was ligated.

During the aforementioned manipulation of the gallbladder, there was no appreciable change in the tone or peristaltic action of the stomach. Croton oil was then applied to the mucosa of the gallbladder by a small cotton swab. After a few minutes there was an increase in the size and depth of the peristaltic waves, comparable to those observed following the application of the irritant to the colon. Here again the induced gastric activity was abolished by atropine.

The investigation at this point was extended to the patient. A balloon was introduced into the pyloric portion of the stomach and connected with a kymograph during a period in which the subject was free from distress. After the gastric activity was recorded for a control period, the colon was inflated through a rectal tube. The tone of the stomach was at once increased; coincidently there was a striking increase in the depth of the peristaltic waves and the appearance of the typical epigastric distress. The pain in each instance occurred simultaneously with the peristaltic waves. Following deflation of the colon, the gastric tone and peristaltic action returned to the original level, and the pain disappeared. Similar results were obtained by atropine without the deflation of the colon. This aspect of the investigation is of particular interest from the standpoint of gastric pain and will be reported more in detail in this connection. It is felt that these results explain the epigastric pain associated with an irritable colon.

COMMENT

The reports here cited of the investigations of the reflex connection between the stomach and the colon have led to diverse conclusions. In the observation of White, and in those of Monroe and Emory, attention was focused on the emptying time of the stomach, and a significant alteration in this feature was not obtained. White indicated that a gastric retention is seldom associated with a pathologic condition of the colon. It was likewise rarely noted in our studies of the gastric manifestation of an irritable colon. It is to be recalled that in the latter study a pyloric spasm and an increase in the peristaltic action of the stomach were the most prominent roentgen observations. In this connection, Hughson reported that a traumatization of any abdominal viscus in the dog by surgical procedure, prolongs the emptying time of the stomach approximately 67 per cent for a period of about two weeks in spite of an increase in the speed of the contraction waves. Clinical and experimental observation therefore indicate that a study of the emptying time of the stomach alone is not a reliable guide in the investigation of the reflex connection between the colon and the stomach. On the other hand, the evidence points to an increase in the tone, particularly of the pyloric portion of the stomach and to an increase in the peristaltic action as the most significant indication of a stimulation from the colon.

The observations of Pearcy and Van Liere appear to be opposed to those made in the present investigation. The character of the stimulation employed is, however, not comparable. The brief periods of inhibition of the gastric contraction shown in their illustrative experiment are similar to those frequently observed in the unanesthetized dog on slight manipulation of the gastro-intestinal tract. These periods

are regarded as transitory and of an entirely different nature than those herewith reported.

In the present investigation, a reflex stimulation of the stomach from the colon, appendix and the gallbladder was demonstrated. This effect which was indicated by an increase in the tone, particularly of the pyloric portion, and by an increase in the depth of the peristaltic waves was completely abolished by atropine. Hughson attributed a similar alteration in the gastric activity to a peritoneal irritation. In the present study, however, all operative procedures incident to the experiment were completed prior to the registration of the control curve, and thus the possibility of an irritation from the peritoneum producing the results was eliminated. These observations on patients are in line with the experimental studies on the dog, and they constitute a further demonstration of the reflex connection between the colon and the stomach.

THE ALKALINE TIDE AS A METHOD OF STUDYING GASTRIC ACIDITY *

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In 1926 a series of tests on the urine of patients suffering from achlorhydria was reported.[1] It was shown that little or no increase in alkalinity developed in such subjects after a standard meal, but that when normal subjects used as controls were studied by the same technic, the urine usually showed an alkaline tide; that is, it became more alkaline than it had been before the meal. The difference between the two types of cases was clearly shown by the average figures. This indicated that the secretion of hydrochloric acid by the stomach was the usual cause of the increase in alkalinity observed, as had been claimed by many observers since Bence-Jones [2] first described these variations in acidity.[3] Similar work by Ackman [4] and Davies [5] has furnished confirmation of this thesis.

In addition to these studies of the physiology involved, it was suggested that the test might be adapted to the indirect study of gastric secretion, and the following procedure was recommended for this purpose. The patient was aroused at 7 o'clock and directed to empty the bladder. This specimen was discarded. Thereafter hourly specimens were collected until 1 p. m. A meal, consisting of two slices of toast, a pat of butter, a glass of milk, a glass of water and an egg, was fed between 8 and 9 o'clock. There were available for analysis six hourly specimens, one collected before the meal, one during the period when the meal was fed and four successive ones following it. The reaction of each was determined soon after it was voided. From a study of the

* Submitted for publication, July 5, 1930.

1. Munford, S. A., and Hubbard, R. S.: The Alkaline Tide in Achlorhydria, J. A. M. A. **87**:922 (Sept. 18) 1926.

2. Bence-Jones, H.: Variations in Earthy and Alkaline Phosphates of the Urine, Phil. Tr., London **135**:335, 1845; cited by Watson: Canad. M. A. J. **15**:32, 1925; Phil. Tr., London **139**:235, 1849; cited by Fiske (footnote 3, first reference).

3. Fiske, C. J.: Observations on the "Alkaline Tide" After Meals, J. Biol. Chem. **49**:163, 1921. Campbell, C. J.: Ammonia Excretion, Amino-Acid Excretion, and the Alkaline Tide in Singapore, Biochem. J. **14**:603, 1920.

4. Ackman, F. D.: The Relations Between Gastric Acidity and the Hydrogen Concentration of the Urine with a Study of the Effect of Histamine, Canad. M. A. J. **15**:1099, 1925.

5. Davies, D. T.: Some Observations on Gastric Secretion and Its Relation to the Urinary Reaction, Brit. J. Exper. Path. **10**:1, 1929.

results it was suggested that if one specimen was more alkaline than any collected previously by 1.0 p_H, or if any two were more alkaline than a previous specimen by 0.5 p_H, a tide was present. If the average reaction was alkaline, that is, if the p_H was greater than 7.0, the test should be regarded as unsatisfactory, because Marshall [6] has shown that the reactions of such specimens cannot be determined accurately. If a tide was present in the urine, it implied that acid was secreted by the stomach. Comparison of the method with the direct analysis of gastric contents showed that there was agreement in about 80 per cent of the studies.

In the present paper the author wishes to discuss the application of this technic in the light of further experience with it, based on a study of 365 tests on 296 subjects. This discussion can conveniently be divided into two parts: first, a consideration of the general forms of the curves obtained, and second, a presentation of individual cases representing the value and limitations of the method.

In general, the results have confirmed the physiologic principal on which the test is based, for the tide shown by normal subjects [7] was quite regularly present when secretion of acid followed the ingestion of a test meal [8] but was absent in cases of achlorhydria. At the same time it became obvious that results were frequently irregular and hard to interpret. An analysis of the various types of curves was made,[9] and it was concluded that there was frequently an early morning period of alkalinity before any meal was fed that affected the test.[10] Table 1 shows the irregularities resulting from the operation of these two causes. Each column gives results obtained by averaging the results obtained from a series of specimens from six different patients, each

6. Marshall, E. K., Jr.: The Effect of Loss of Carbon Dioxide on the Hydrogen Ion Concentration of Urine, J. Biol. Chem. **51**:3, 1922.

7. Wilson, D. W.: Neutrality Regulation in the Body, Physiol. Rev. **3**:295, 1623. Hubbard, R. S., and Munford, S. A.: Presence of the "Alkaline Tide," J. A. M. A. **80**:304 (Feb. 3) 1923. Muschat, M.: The Effect of Changes in Regime upon the Urine Alkaline Tide in Normal Individuals, J. Clin. Investigation **2**:245, 1925. Hubbard, R. S., and Steele, T. M.: Variations in the Morning Alkaline Tide of Normal Individuals, J. Biol. Chem. **84**:199, 1929.

8. Rehfuss, M. E.: A New Method of Gastric Testing, with a Description of a Method for the Fractional Testing of the Gastric Juice, Am. J. M. Sc. **147**: 848, 1914. Lyons, B. B. V.; Barth, H. J., and Ellison, R. T.: Clinical Gastric Analysis with Detail of Method and a Consideration of the Maximum Information to be Obtained, New York M. J. **114**:272, 1921.

9. Hubbard, R. S.: The Reaction of the Morning Urine, J. Biol. Chem. **84**:191, 1929.

10. Leathes, J. B.: Renal Efficiency Tests in Nephritis and the Reaction of the Urine, Brit. M. J. **2**:165, 1919; Renal Function, a Determination of Its Degree, Lancet **2**:933, 1920. Watson, E. M.: The Cause of the Matutinal Tide in Urine, Canad. M. A. J. **15**:32, 1925. Hubbard, R. S.: Changes in the Reaction of Urine on Awakening, Am. J. Physiol. **91**:618, 1930.

one of which was closely like the other five. Column I shows the flat curve with a rather high degree of acidity frequently found in cases of achlorhydria. Superimposed on this there is not infrequently an early period of alkalinity (column II) that is often prolonged well into the morning (column III). Results typical of those expected if the stomach secretes hydrochloric acid are given in column IV. Here there is no early morning period of alkalinity, but changes similar to those expected if the stomach secreted hydrochloric acid develop after the meal is fed, and an alkalinity of the urine results from the changes in the body fluids produced. Results in column V are essentially similar and can easily be interpreted, although the figures are not quite as regular as those just discussed. It is evident that if there are two normal causes of a decreased acidity in morning urine they must fre-

TABLE 1.—*Irregularities Due to Achlorhydria and an Early Morning Period of Alkalinity* *

Hour	I 0 Hydrochloric Acid p_H	II 0 Hydrochloric Acid p_H	III 0 Hydrochloric Acid p_H	IV Hydrochloric Acid + p_H	V Hydrochloric Acid + p_H	VI Hydrochloric Acid + p_H	VII Hydrochloric Acid + p_H	VIII Hydrochloric Acid + p_H
Before meal.....	5.4	6.3	7.3	5.4	5.6	7.1	7.5	7.8
Meal time.....	5.4	5.3	6.9	5.9	5.6	5.9	7.6	7.8
0 to 1 after.....	5.4	5.3	6.1	6.2	5.7	5.7	6.1	7.6
1 to 2 after.....	5.3	5.3	5.7	7.4	6.9	6.3	7.3	7.6
2 to 3 after.....	5.4	5.3	5.4	6.9	6.9	7.1	7.5	7.8
3 to 4 after.....	5.3	5.3	5.4	5.9	5.4	6.4	6.9	7.6

* Each column gives the results obtained by averaging a series of specimens from six different specimens.

quently operate in the same patient. Column VI contains results that illustrate this fact. Figures of this kind are not difficult to interpret, because the early morning period of alkalinity can be quite clearly differentiated from the one that follows the meal. Sometimes, however, the two curves seem to fuse more or less completely. Examples are given in column VII, in which a single specimen with an acid reaction separates two periods of marked alkalinity, and in column VIII in which the reaction is uniformly alkaline throughout. Such results, when obtained in any particular case, are hard to interpret in terms of the clinical condition of the patient, for while in general they seem to be due to the aforementioned causes, in any given case the same results may be brought about in an entirely different manner.[11] If the activity of the patient is reduced by keeping him in bed, and respiratory

11. Hubbard, R. S., and Allison, C. B.: A Study of Continued Alkalinity of Morning Urine, Proc. Soc. Exper. Biol. & Med. **27**:212, 1929; Clifton M. Bull. **16**:6, 1930.

variations, which form one of the causes of variations in urinary acidity,[12] are thus reduced to a minimum, anomalous results are still encountered.[13]

It is obvious from the preceding discussion that results that cannot be interpreted or that can be interpreted only with considerable uncertainty are not infrequent. It seems worth while to present also a series of selected cases illustrating the various types of observations to show the value and limitations of the method when the results are characteristic. For this purpose cases in which the results of studies with histamine [14] were available have been selected. Since histamine is used in this clinic only when routine gastric analysis shows the absence of hydrochloric acid, and since in general determinations of the alkaline tide were not carried out except when the presence of achlorhydria was suspected, no strictly normal case is included in the series. For such results the reader is referred to previous publications,[15] and to table 1, columns IV and V. The series does include complete concordant results in a case of achlorhydria, and these results are given in table 2. The urine of this patient showed no change in reaction during the morning period, and no acid was secreted into the stomach under the stimulus of any of the methods used.

The case summarized in table 3 also shows satisfactory agreement among the three methods of studying gastric acidity. No hydrochloric acid was present in the stomach an hour and a half after a test meal, but an hour after histamine was given a trace of the free acid could be detected. In the study of the alkaline tide a slight increased alkalinity was found in one specimen obtained after the meal. This change was so slight that no significance can properly be attached to it, and, according to the criteria laid down in the preceding article,[1] no tide was present. It is obvious that such results must be expected when the gastric acidity is as low as in this case.

12. Collip, J. B., and Backus, P. L.: The Effect of Prolonged Hyperpnoea on the Carbon Dioxide Combining Power of the Plasma, the Carbon Dioxide Tension of the Alveolar Air, and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney, Am. J. Physiol. **51**:568, 1920. Grant, S. B., and Goldam, A.: A Study of Forced Respiration: Experimental Production of Tetany, Am. J. Physiol. **52**:209, 1920.

13. Hubbard, R. S., and Steele, T. M. (footnote 7, fourth reference).

14. Dobson, H. V.: Effect of Histamin on Gastric Secretion, J. A. M. A. **84**:158 (Jan. 17) 1925. Schneider, J. P., and Carey, J. B.: The Clinical Significance of Primary Achlorhydria, J. A. M. A. **91**:1763 (Dec. 8) 1928.

15. Hubbard, R. S.; Munford, S. A., and Allen, E. G.: Gastric Secretion and the Alkaline Tide in Urine, Am. J. Physiol. **68**:207 (Nov. 23) 1924. Hubbard, R. S., and Allen, E. G.: Simultaneous Determinations of Gastric Acidity and the Alkaline Tide in Urine, Arch. Int. Med. **35**:586 (May) 1925.

The third case, shown in table 4, is an example of those cases in which a study of the tide gives more reliable information than an analysis of the gastric contents after the usual test meal. Another similar case has been reported previously.[16] The results of a gastric analysis suggested that the stomach did not secrete hydrochloric acid,

TABLE 2.—*Complete Concordant Results in Gastric Analysis and Alkaline Tide Test in a Case of Achlorhydria*

Gastric Analysis			Histamine Test		
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.
0	0	15	0	0	9
30	0	7	20	0	7
45	0	5	40	0	8
60	0	6	60	0	6
75	0	8	1.5 mg. ergamine* phosphate used		
105	0	9			
135	0	?			

Alkaline Tide Test †

	Time					
	7-8	8-9	9-10	10-11	11-12	12-1
pH	5.4	5.3	5.3	5.3	5.3	5.5

* Ergamine is beta-iminazolylethylamine hydrochloride.
† Results of gastric studies are expressed as cubic centimeters of tenth-normal acid in 100 cc. gastric contents.

TABLE 3.—*Showing Agreement of Gastric Analysis and Alkaline Tide Test*

Gastric Analysis*			Histamine Test		
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.
75	0	12	0	0	16
			20	0	18
			40	0	23
			60	5	27
			1.5 mg. ergamine phosphate used		

Alkaline Tide Test

	Time					
	7-8	8-9	9-10	10-11	11-12	12-1
pH	5.2	5.0	5.0	5.7	5.2	5.0

* Results of gastric studies are expressed as cubic centimeters of tenth-normal acid in 100 cc. gastric contents. The gastric specimen was obtained through a large tube passed after an Ewald test meal.

although the high figures obtained when the total acid was determined make such an interpretation questionable. When histamine was given, free hydrochloric acid was found in normal concentration. I believe that two causes may lead to such results. If the stomach produces acid but it is neutralized by alkaline secretions or mucus, the urine should

16. Hubbard, R. S.: Variations in Gastric Acidity and in the Alkaline Tide in Urine, a Discussion of a Case, Clifton M. Bull. **14**:7, 1928.

nevertheless show the normal tide. Another possibility is that the secretion of hydrochloric acid has been completely inhibited by some influence induced by the presence of the tube,[17] but that secretion may proceed normally when no tube is present, and that, therefore, there may be a normal tide.

When a typical alkaline tide is present in a case apparently showing achlorhydria, the gastric analysis should be questioned and careful investigations carried out before a diagnosis is made. Can the alkaline tide observations be accepted as of final value under such conditions? The answer to this question is probably no, as far as one can tell at present. My associates and I have found very few cases—three at most

TABLE 4.—*Case in Which Study of the Alkaline Tide Gave More Accurate Information Than Analysis of the Gastric Contents After the Usual Test Meal*

Gastric Analysis			Histamine Test*		
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.
0	0	?	0	0	5
30	0	11	20	0	10
45	0	40	40	36	58
60	0	30	60	31	50
75	0	25	1.5 mg. ergamine phosphate used		
105	0	19			
135	0	?			

Alkaline Tide †

	Time					
	7-8	8-9	9-10	10-11	11-12	12-1
p_H	5.3	5.3	6.1	6.2	6.6	5.8

* Histamine test and alkaline tide test agree.
† Results of gastric studies are expressed as cubic centimeters of tenth-normal acid in 100 cc. of gastric contents.

—when such an interpretation would probably have been incorrect. In these three cases fairly typical alkaline tides were present in the urine, but no hydrochloric acid was found in the contents of the stomach after histamine was injected. None of these cases has shown the clean-cut clinical picture frequently seen in achylia gastrica.[18] It seems proper, nevertheless, to accept them as true cases of achlorhydria until such indirect studies as have been carried out in the clinic can be confirmed by some other method of investigation. Fairly complete experiments showing such contradictory results have been carried out on one patient and reported elsewhere.[19] Studies in another case are given

17. Kahn, G., and Stokes, J., Jr.: The Effect of the Passage of the Stomach Tube on Titratable Acidity and p_H of Gastric Contents, Am. J. Dis. Child. **32:** 667 (Nov.) 1926.

18. Collip and Backus (footnote 12, first reference).

19. Hubbard, R. S., and Case, C. E.: Presence of the Alkaline Tide in a Case of Achlorhydria, Proc. Soc. Exper. Biol. & Med. **27:**327, 1930.

in table 5. The tide obtained was not wholly satisfactory but it suggested that the stomach secreted hydrochloric acid, while all of the direct studies carried out failed to show any formation of that compound. No adequate explanation can be offered for such observations. Either the direct methods used for studying gastric secretion are not wholly satisfactory—I do not believe that there is sufficient evidence to justify such a conclusion—or there may be some cause independent of the secretion of hydrochloric acid by the stomach that sometimes produces changes in urinary reaction that are indistinguishable from those considered as typical tides. A few experiments suggest that the second alkaline tide of the day—that which follows the noon meal—may give more reliable information concerning the presence or absence of gastric secretion than does the first one, but at present the number of studies

TABLE 5.—*Contradictory Results Obtained in the Same Patient*

Gastric Analysis			Histamine Test*		
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.
0	0	9	0	0	5
20	0	5	20	0	8
45	0	6	40	0	10
60	0	4	60	0	8
75	0	5	1.5 mg. ergamine phosphate used		
105	0	9			
135	0	10			

Alkaline Tide Test†

	Time					
	7-8	8-9	9-10	10-11	11-12	12-1
*p*H	...	6.1	6.2	...	7.1	7.4

* Gastric analysis and histamine test agree.
† Results are expressed as cubic centimeters of tenth-normal acid per 100 cc. gastric juice.

available are too few to serve as a basis for conclusions on their significance.

Errors of the opposite sort, the absence of a tide when the stomach secretes hydrochloric acid, are present in about 20 per cent of the cases studied. One large group of patients in whom such observations were made, were subjects with various conditions affecting gastric secretion. There may be so marked a degree of hypochlorhydria that variations in the acid-base balance in the body are so slight that no changes in the reaction of the urine result from it. An essentially similar condition exists when the concentration of hydrochloric acid is normal but the amount of fluid secreted is small. Here again little variation in the reaction of the body fluids may result from gastric secretion, because those changes depend on the actual amount of acid withdrawn from the tissues and the resultant liberation of an approximately equivalent amount of base in them. A third group of cases in which discrepancies of this sort are easily understood includes those in which there is a

very rapid gastric emptying time. In these the acid material probably enters the intestine and is once more reabsorbed soon after it is formed, so that changes in the reaction of the tissues is of short duration.

Besides such cases as these in which the conditions governing secretion and reabsorption of hydrochloric acid probably influence the results, there are certain diseases that may cause an absence of a tide in a subject with normal gastric acidity. One of these diseases is cystitis. Persons suffering from this condition are not suitable subjects for the test, because the reaction of the urine may result from the action of bacteria in the bladder rather than from variations in the acid-base balance in the body. Nephritis may also apparently sometimes give rise to misleading results. Leathes [20] and McCorvie [21] have shown that in this condition the reaction of the urine does not respond in the usual way to variations in the conditions in the blood. Whether there are other factors that may seriously affect the reaction of the urine in a similar way, remains uncertain. Among the possibilities is the modifying influence of the phosphates present as buffers in the urine. The work on this subject recently reviewed by Rannenberg [22] suggests that variations in the amounts of these compounds may sometimes be of importance in modifying the reaction of the urine.

CONCLUSION

A study of the urine in a series of cases has shown that the presence or absence of an alkaline tide may frequently be of aid in the study of gastric conditions. When a tide is present after a meal, hydrochloric acid can almost always be demonstrated in the gastric juice. In about 80 per cent of those subjects who do not show an alkaline tide, hydrochloric acid is either absent from the gastric juice or is present in very low concentration.

Certain limitations exist to the usefulness of the test. It seems to be impossible to distinguish between a normal secretion and a hypersecretion of hydrochloric acid by this method.[23] It is frequently difficult to interpret the results obtained because of their irregular nature. The test is valueless in cystitis and nephritis. Apparently the alkaline tide should not be relied on alone to distinguish between the true and false achylia; however, if a tide is present, such a diagnosis should be made only after thorough study, including the use of histamine.

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20. Leathes (footnote 10, first and second references).

21. McCorvie, J. E.: Studies on the Morning Alkaline Tide of Urine in Normal Persons and in Patients with Nephritis, J. Clin. Investigation **2**:35, 1925.

22. Rannenberg, E.: Die Schwankungen der Wasserstoffionenkonzentration des Harns im Verlaufe eines Tages, Arch. f. d. ges. Physiol. **212**:601, 1926.

23. Dodds, E. C.: Variations in Some of the Urinary Constituents and the Alveolar CO_2 in Relation to Meals, Brit. J. Exper. Path. **4**:13, 1923.

METABOLISM OF OBESITY

VIII. BASAL METABOLISM AND INSENSIBLE PERSPIRATION DURING A PERIOD OF REDUCING WEIGHT *

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Owing to the lack of adequate provisions for prolonged metabolic work on adults during a period of reducing weight, our previous studies of this series had been made on outpatients only. An extensive investigation was conducted on three obese women, one with diabetes, during a period of eight months in 1928. The subjects were kept in a special ward provided with a kitchenette and facilities for collecting and storing excreta. They were given freedom to lead a normal life and were permitted to go about as they pleased. However, they were under the constant supervision of an attendant assigned to this task. At no time were they allowed free access to foods.

During the experimental period the subjects received a diet containing 20 Gm. of butter per twenty-four hours, 1 Gm. of protein and sufficient carbohydrate to make a total of 20 calories per kilogram of ideal weight per twenty-four hours. Based on our investigations conducted on a number of normal women, the foregoing diet should contain approximately 50 per cent of the caloric value required by these subjects according to their ideal weights. In the case of the subject with diabetes, sufficient insulin was given to keep her urine always free from sugar; the dosage varied from 30 units at the beginning to 8 units at the end of the experiment. As this subject demonstrated a rapid decrease in basal metabolism in the course of reducing weight, she was also given thyroid treatment during the latter part of the experiment.

This investigation covered the determination of basal metabolism, insensible perspiration, water balance and protein metabolism of the three subjects. The present paper deals with the basal metabolism and the insensible perspiration. The chemical procedure and the results of the latter half of the investigation will be reported in a later communication.

* Submitted for publication, April 23, 1930.

* From the Medical Clinic and the Nelson Morris Memorial Institute for Medical Research of Michael Reese Hospital. Aided by the Otto Baer Fund and the fund contributed jointly by Judge Hugo Pam and Miss Carrie Pam.

TABLE 1.—*Daily Basal Heat Production*

Subject: E. S.; height, 150.9 cm.; age, 35 years; normal weight, 55.9 Kg.

Date	Weight			Heat Production							
	Kg.	Daily Variation, Kg.	Percentage Over Normal Weight	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate	Thyroid Extract, Gr.
Aug. 2	80.3	.....	43.5	0.719	38.2	+ 3.4	1,662	+ 8.1	20.7	76	...
3	79.7	—0.7	42.5	0.697	41.6	+15.1	1,751	+14.2	22.0	78	...
4	79.4	—0.2	42.1	0.745	39.0	+ 5.4	1,638	+ 7.1	20.6	68	...
6	79.6	+0.1	42.3	0.670	35.5	— 4.0	1,494	— 2.5	18.8	66	...
7	79.7	+0.1	42.5	0.640	39.7	+ 8.0	1,670	+ 8.9	21.0	72	...
8	79.2	—0.5	41.7	0.689	39.7	+ 7.3	1,666	+ 8.9	21.0	66	...
9	79.4	+0.2	42.1	0.731	36.3	— 1.6	1,525	— 0.3	19.2	66	...
10	79.4	±0.0	42.1	0.720	36.2	— 2.0	1,522	— 0.5	19.2	68	...
11	79.3	—0.1	41.9	0.695	36.1	— 2.5	1,516	— 0.8	19.1	66	...
13	78.7	—0.4	40.8	0.739	32.3	—12.6	1,356	—11.0	17.0	66	...
14	78.4	—0.3	40.3	0.781	34.5	— 6.8	1,441	— 5.3	18.4	78	...
Sept. 26	80.3	.....	43.5	0.765	38.1	+ 3.0	1,609	+ 4.6	20.0	70	...
27	80.1	—0.2	43.3	0.762	35.6	— 3.8	1,504	— 2.1	18.8	72	...
28	79.6	—0.5	42.5	0.731	37.0	± 0.0	1,553	+ 1.4	19.5	72	...
29	79.5	—0.1	42.3	0.790	39.9	+ 7.8	1,667	+ 8.9	21.1	72	...
Oct. 1	79.7	+0.2	42.7	0.783	32.8	—11.7	1,382	— 9.9	17.3	72	...
2	79.7	—0.1	42.5	0.721	36.2	— 2.2	1,522	— 0.8	19.0	76	...
3	79.9	+0.2	42.9	0.650	33.6	— 9.2	1,413	— 7.9	17.7	70	...
4	79.6	—0.2	42.5	0.726	36.3	— 1.9	1,523	— 0.6	19.1	68	...
5	79.5	—0.1	42.3	0.774	32.4	—12.5	1,360	—11.1	17.1	62	...
6	79.4	—0.1	42.1	0.689	33.3	—10.1	1,398	— 9.4	17.6	62	...
8	79.4	±0.0	42.1	0.735	31.9	—13.8	1,336	—12.7	16.8	62	...
9	78.1	—1.4	39.7	0.728	31.9	—13.7	1,332	—12.7	17.0	62	...
10	78.3	+0.2	40.1	0.722	29.8	—19.4	1,296	—15.2	16.6	64	...
12	78.3	0.0	40.1	0.706	32.5	—12.3	1,355	—11.4	17.3	62	...
13	78.4	+0.1	40.3	0.725	30.8	—16.8	1,284	—15.6	16.4	60	...
15	78.3	—0.1	40.0	0.787	31.8	—14.0	1,360	—11.1	17.2	58	...
16	78.1	—0.2	39.7	0.698	31.3	—15.5	1,308	—14.2	16.8	60	...
17	78.0	—0.1	39.4	0.733	30.3	—18.2	1,263	—16.7	16.2	56	...
18	77.8	—0.1	39.2	0.682	31.9	—13.8	1,328	—12.3	17.1	64	...
19	77.0	—0.8	37.8	0.693	27.9	—24.5	1,163	—22.9	15.1	60	...
20	76.9	—0.1	37.6	0.744	31.3	—15.3	1,299	—13.8	16.9	56	...
22	77.6	+0.7	38.8	0.773	31.2	—15.6	1,314	—13.3	16.9	56	...
23	76.9	—0.7	37.6	0.743	29.1	—21.4	1,220	—19.0	15.9	58	...
24	77.4	+0.5	38.4	0.734	31.6	—14.6	1,314	—13.0	17.0	58	...
25	77.6	+0.2	38.8	0.736	31.0	—16.3	1,288	—19.0	16.6	58	...
26	77.5	—0.1	38.6	0.729	32.5	—12.3	1,350	—10.7	17.4	64	...
27	76.9	+0.1	37.6	0.783	28.5	—22.9	1,181	—20.6	15.4	64	...
29	76.6	—0.3	37.0	0.766	31.2	—15.8	1,287	—14.4	16.8	56	...
30	76.5	—0.1	36.8	0.774	31.9	—13.9	1,318	—12.4	17.2	56	...
31	75.9	—0.6	35.8	0.753	30.3	—18.2	1,247	—16.7	16.4	58	...
Nov. 1	76.1	+0.2	36.2	0.719	30.4	—17.7	1,297	—13.5	17.0	60	...
2	76.2	+0.1	36.4	0.748	31.6	—14.6	1,304	—13.1	17.1	58	...
3	75.8	—0.5	35.6	0.767	33.6	— 9.1	1,369	— 8.4	18.1	64	...
5	75.4	—0.4	35.0	0.697	29.5	—20.4	1,210	—19.6	16.0	54	...
6	75.3	—0.1	34.8	0.801	33.2	—10.4	1,363	— 8.6	18.1	64	...
7	75.6	+0.2	35.2	0.766	29.8	—19.7	1,226	—18.2	16.2	54	...
8	75.2	—0.3	34.6	0.771	29.8	—19.4	1,228	—17.6	16.3	54	...
9	75.3	+0.1	34.7	0.790	30.5	—17.6	1,252	—16.0	16.6	54	...
12	75.8	+0.5	35.4	0.732	31.7	—14.4	1,292	—13.6	17.1	52	1
13	75.9	+0.1	35.8	0.736	31.4	—15.1	1,294	—13.6	17.1	52	1
14	75.2	—0.7	34.6	0.773	31.1	—15.9	1,280	—14.1	17.0	54	1
15	74.5	—0.7	33.3	0.746	32.8	—11.4	1,340	— 9.0	18.0	54	1
16	74.2	—0.3	32.7	0.723	30.9	—16.5	1,262	—14.7	17.0	50	1
17	74.1	—0.1	32.5	0.793	30.4	—17.8	1,241	—16.1	16.8	58	1
19	73.9	—0.2	32.3	0.736	30.9	—16.6	1,259	—15.6	17.0	60	1
20	73.5	—0.4	31.5	0.722	33.0	—10.4	1,342	— 9.5	18.3	58	1
21	73.6	+0.1	31.6	0.745	29.9	—16.4	1,219	—17.3	16.6	56	1
22	73.3	—0.3	31.1	0.742	33.4	— 9.6	1,327	— 9.9	18.1	58	1
23	73.1	—0.2	30.7	0.818	31.4	—15.1	1,271	—13.5	17.4	54	1
24	72.9	—0.1	30.5	0.760	31.3	—15.5	1,268	—13.6	17.4	62	1
26	73.1	+0.1	30.7	0.768	31.1	—15.8	1,263	—14.1	17.3	60	1
27	73.2	+0.1	30.9	0.775	33.3	—10.1	1,349	— 8.2	18.4	62	1
28	73.6	+0.4	31.6	0.781	32.4	—12.5	1,315	—10.8	17.9	60	1
30	73.1	—0.5	30.7	0.761	32.5	—12.3	1,316	—10.5	18.0	64	1
Dec. 1	72.5	—0.6	29.7	0.739	31.8	—14.0	1,279	—12.1	17.9	62	1
3	72.9	+0.5	30.5	0.732	31.6	—14.7	1,281	—12.7	17.6	58	1
4	72.7	—0.2	30.1	0.768	31.9	—13.8	1,288	—12.1	17.7	58	1
5	72.6	—0.1	29.9	0.739	30.9	—16.6	1,249	—14.7	17.2	58	1
6	72.4	—0.2	29.5	0.794	29.3	—20.5	1,184	—19.1	16.4	54	1
7	72.6	+0.2	29.9	0.819	30.4	—17.8	1,230	—16.0	16.9	60	1

TABLE 1.—*Daily Basal Heat Production—Continued*

Subject: E. S.; height, 150.9 cm.; age, 35 years; normal weight, 55.9 Kg.

Date	Weight			Heat Production							
	Kg.	Daily Variation, Kg.	Percentage Over Normal Weight	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate	Thyroid Extract, Gr.
Dec. 8	72.4	—0.2	29.5	0.721	32.9	—11.3	1,330	—10.0	18.4	54	1
10	72.3	—0.1	29.3	0.733	31.6	—14.6	1,273	—13.0	17.6	62	2
11	72.4	+0.1	29.5	0.746	33.6	— 9.1	1,358	— 7.5	18.8	66	2
12	72.2	—0.2	29.1	0.749	33.9	— 8.3	1,369	— 6.4	19.0	62	2
13	72.5	+0.3	29.7	0.761	35.8	— 3.2	1,439	— 1.1	19.9	64	2
15	72.3	—0.2	29.3	0.735	36.2	— 2.1	1,463	± 0.0	20.2	74	2
26	71.8	.....	28.4	0.867	35.1	— 5.2	1,406	— 3.6	19.6	62	2
27	70.9	—0.9	26.8	0.832	34.3	— 6.9	1,377	— 5.0	19.4	58	2
28	70.9	±0.0	26.8	0.884	34.6	— 6.4	1,387	— 4.3	19.6	56	2
29	70.7	—0.2	26.4	0.781	36.7	— 0.8	1,468	+ 1.5	20.8	68	2
31	70.1	—0.6	25.4	0.860	34.3	— 7.2	1,368	— 5.1	19.5	68	2
Jan. 2	69.8	—0.4	24.8	0.798	35.1	— 5.1	1,397	— 2.9	20.0	74	2
3	69.8	±0.0	24.8	0.785	35.8	— 3.3	1,423	— 1.1	20.4	70	2
4	69.5	—0.2	24.4	0.701	35.9	— 3.1	1,424	— 0.8	20.5	76	...
5	69.2	—0.3	23.8	0.779	37.1	+ 0.2	1,470	+ 2.6	21.2	72	...
7	69.3	+0.1	24.0	0.779	35.9	— 3.1	1,422	— 0.8	20.5	66	...
8	69.3	±0.0	24.0	0.726	39.2	+ 6.0	1,555	+ 8.4	22.4	72	...
9	69.5	+0.2	24.4	0.719	38.8	+ 4.9	1,541	+ 7.2	22.2	72	...

During the period of reducing weight, the study of basal metabolism of the three subjects, including eighty-nine experiments on one and seventy-three on another, was made within four months. Twenty-eight experiments were conducted on the third subject during an interval of a month. An attempt was made to take daily observations, but owing to the lack of cooperation on the part of the subjects, the work was interrupted frequently. Consequently, no observations were made on Sundays or on days when for various reasons the patients were in a contradictory mood and offered excuses for not taking the test. At the beginning of the experiment the weights of the three subjects were 80.3, 95 and 108.4 kilograms, with a deviation from standard of 43.5, 54.7 and 95.4 per cent, respectively. The ages were 35, 23 and 21 years.

Heat production was measured by a Tissot gasometer in connection with a Haldane gas analysis apparatus as described in a previous communication.[1] All experiments were conducted after a fast of at least fourteen hours and a rest period of thirty minutes.

1. Strouse, S.; Wang, C. C., and Dye, M.: Studies on the Metabolism of Obesity: II. Basal Metabolism, Arch. Int. Med. **34**:275 (Sept.) 1924.

TABLE 2.—*Daily Basal Heat Production*

Subject: C. B.; height, 168.9 cm.; age, 23 years; normal weight, 61.4 Kg.

	Weight			Heat Production						
Date	Kg.	Daily Variation, Kg.	Percentage Over Normal Weight	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate
May 24	95.0	.....	54.7	0.877	33.6	— 9.1	1,655	— 6.2	17.4	72
25	94.3	—0.7	53.6	0.728	35.2	— 4.8	1,732	— 1.4	18.4	70
26	94.3	±0.0	53.6	0.746	33.9	— 8.3	1,665	— 5.2	17.7	65
28	94.8	+0.5	54.4	0.765	31.0	—16.3	1,523	—13.6	16.1	64
29	94.2	—0.6	53.4	0.874	31.4	—15.2	1,539	—12.4	16.3	65
30	94.2	±0.0	53.4	0.786	34.7	— 6.2	1,701	— 3.0	18.1	64
31	93.8	—0.4	52.8	0.797	36.2	— 2.1	1,777	+ 1.3	19.0	64
June 1	94.1	+0.3	53.3	0.792	34.1	— 7.7	1,678	— 4.4	17.8	62
2	93.6	—0.5	52.4	0.792	34.2	— 7.5	1,675	— 4.3	17.9	62
4	93.0	—0.6	51.5	0.779	31.5	—15.0	1,534	—12.0	16.5	62
5	93.0	±0.0	51.5	0.808	33.7	— 9.0	1,642	— 5.9	17.7	60
6	92.8	—0.2	51.1	0.752	32.2	—13.0	1,571	— 9.2	16.9	62
7	93.0	+0.2	51.5	0.833	35.3	— 4.5	1,723	— 1.2	18.5	62
8	93.3	+0.3	52.0	0.765	35.1	— 5.2	1,713	— 1.9	18.4	62
9	93.3	±0.0	52.0	0.861	36.7	— 0.9	1,776	+ 1.1	19.0	60
11	91.8	—1.5	49.5	0.808	34.2	— 7.5	1,659	— 4.3	18.1	60
12	91.4	—0.4	48.9	0.755	33.6	— 9.3	1,630	— 5.7	17.8	62
13	91.5	+0.1	49.0	0.778	32.8	—11.3	1,589	— 8.2	17.4	60
14	91.6	+0.1	49.2	0.781	32.1	—13.1	1,557	—10.1	17.0	..
15	91.8	+0.2	49.5	0.739	33.2	—10.3	1,610	— 7.1	17.5	56
16	91.8	±0.0	49.5	0.719	35.5	— 4.1	1,723	— 0.8	18.8	60
18	91.5	—0.3	49.0	0.732	34.8	— 5.8	1,687	— 2.5	19.2	60
19	91.1	—0.4	48.4	0.766	34.7	— 6.3	1,675	— 3.1	18.4	58
20	90.7	—0.4	47.7	0.776	32.7	—11.1	1,577	— 8.9	17.4	58
21	91.0	+0.3	48.2	0.719	30.7	—17.0	1,483	—14.0	16.3	60
23	89.5	—1.5	45.8	0.769	32.8	—11.4	1,572	— 8.1	17.6	56
25	89.4	—0.1	45.6	0.735	36.3	— 1.8	1,742	+ 1.8	19.5	59
26	89.9	+0.5	46.4	0.782	33.6	— 9.2	1,615	— 6.3	18.0	60
27	90.1	+0.2	46.7	0.778	36.3	— 2.0	1,744	+ 1.0	19.4	62
28	90.0	—0.1	46.7	0.757	36.7	— 0.8	1,780	+ 3.2	19.8	60
29	89.6	—0.4	45.9	0.784	35.8	+ 3.9	1,830	+ 6.3	20.4	54
30	89.2	—0.2	45.3	0.750	37.3	+ 0.9	1,788	+ 4.6	20.0	54
July 2	88.6	—1.6	44.3	0.761	34.7	— 6.3	1,654	— 2.9	18.8	60
5	87.6	—1.0	42.7	0.744	37.7	+ 1.8	1,787	+ 5.6	20.4	58
7	87.1	—0.5	41.9	0.772	36.9	— 0.4	1,749	+ 2.5	20.1	64
9	86.6	—0.5	41.0	0.778	34.5	— 6.8	1,640	— 1.6	18.9	60
10	86.9	+0.3	41.5	0.751	37.6	+ 1.5	1,779	+ 6.1	20.5	70
11	87.0	+0.1	41.7	0.801	31.7	—15.3	1,503	—10.9	17.3	62
12	87.5	+0.5	42.5	0.778	33.9	— 8.5	1,602	— 5.3	18.3	58
18	85.9	—1.6	39.9	0.723	34.3	— 7.4	1,614	— 4.1	18.8	58
19	85.2	—0.7	38.8	0.734	33.9	— 8.5	1,591	— 4.7	18.8	62
20	86.1	+0.9	40.3	0.840	36.9	— 0.4	1,740	+ 3.6	20.2	66
21	86.0	—0.1	40.1	0.788	34.6	— 6.4	1,638	— 2.4	19.1	68
23	85.5	—0.5	39.3	0.830	36.8	— 0.4	1,733	+ 3.6	20.3	64
24	85.5	±0.0	39.3	0.777	33.1	— 7.9	1,556	— 1.0	18.2	54
25	85.1	—0.4	38.7	0.766	40.0	+ 8.1	1,876	+11.9	22.1	58
26	85.4	+0.3	39.1	0.796	33.4	— 6.9	1,581	— 5.4	18.5	56
27	85.3	—0.1	38.9	0.782	34.2	— 7.5	1,609	— 3.8	18.9	54
28	85.1	—0.2	38.7	0.772	34.8	— 6.0	1,636	— 2.0	19.2	54
30	85.5	+0.4	39.3	0.723	35.6	— 3.9	1,674	± 0.0	19.6	54
31	85.2	—0.3	38.8	0.735	34.9	— 5.5	1,643	— 1.9	19.5	58
Aug. 16	84.4	.....	37.5	0.737	33.9	— 8.5	1,582	— 4.8	18.7	63
17	83.5	—0.9	36.0	0.768	31.9	—13.7	1,483	—10.3	17.8	60
18	83.6	+0.1	36.2	0.783	37.0	± 0.0	1,723	+ 4.1	20.6	58
20	83.1	—0.5	35.4	0.794	40.2	+ 8.9	1,878	+13.8	22.6	68
22	81.8	—1.3	33.2	0.765	34.5	— 9.4	1,594	— 2.6	19.5	60
27	81.0	—0.8	31.9	0.699	30.3	—18.2	1,392	—14.7	17.2	60
28	81.8	+0.8	33.2	0.717	39.7	+ 7.3	1,834	+12.0	22.4	55
31	81.4	—0.5	32.5	0.724	30.5	—17.6	1,419	—13.1	17.4	55
Sept. 1	81.0	—0.3	32.0	0.725	32.4	—12.6	1,499	— 8.0	18.5	56
4	81.1	+0.1	32.2	0.755	32.2	—13.0	1,499	— 8.1	18.5	56
5	81.0	—0.1	32.0	0.732	33.4	— 9.7	1,548	— 5.0	19.1	54
6	80.8	—0.2	31.6	0.701	33.0	—10.9	1,519	— 6.7	18.8	55
7	81.1	+0.3	32.2	0.724	31.9	—13.9	1,484	— 9.0	18.3	56
8	80.7	—0.5	31.4	0.735	33.6	— 9.1	1,548	— 4.9	19.2	59
13	80.4	—0.2	31.0	0.748	33.8	— 8.9	1,557	— 4.1	19.4	58
14	81.2	+0.7	32.2	0.731	33.6	— 9.2	1,549	— 5.1	19.1	56
17	80.0	—1.2	30.3	0.737	35.6	— 3.1	1,629	+ 0.6	20.4	62
18	79.7	—0.3	29.9	0.723	34.9	— 5.6	1,598	— 0.6	20.0	58
19	79.2	—0.5	29.0	0.768	36.5	— 1.7	1,665	+ 2.7	21.0	60
20	79.2	±0.0	29.0	0.706	38.1	+ 2.7	1,737	+ 7.8	21.9	56
21	79.0	—0.2	28.6	0.706	34.4	— 7.2	1,558	— 3.3	19.7	60
22	79.7	+0.7	29.7	0.726	37.2	+ 0.5	1,695	+ 4.8	21.4	56

TABLE 3.—*Basal Heat Production*

Subject: H. M.; height, 159.4 cm.; age, 21 years; normal weight, 55.5 Kg.

	Weight			Heat Production						
Date	Kg.	Daily Variation, Kg.	Percentage Variation Over Normal	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate
May 29	108.4	.....	95.4	0.688	37.5	+ 1.4	1,880	— 0.5	17.4	70
30	108.4	±0.0	95.4	0.681	37.2	+ 0.5	1,865	— 1.2	17.2	68
31	108.0	—0.4	94.6	0.736	35.4	— 4.3	1,768	— 6.2	16.4	66
June 1	107.6	—0.4	93.9	0.734	35.0	— 5.3	1,750	— 7.0	16.3	65
2	107.6	±0.0	93.9	0.741	33.4	— 9.8	1,666	—11.4	15.5	66
4	107.0	—1.0	92.8	0.715	34.9	— 5.7	1,736	— 7.4	16.2	64
5	107.0	±0.0	92.8	0.732	33.8	— 8.6	1,683	—10.2	15.2	66
6	107.0	±0.0	92.8	0.700	35.5	— 4.2	1,764	— 5.9	16.5	66
7	107.2	+0.2	93.2	0.708	33.2	—10.3	1,652	—12.0	15.4	68
9	105.8	—1.4	90.7	0.699	34.8	— 6.0	1,727	— 7.4	16.3	66
11	106.5	—0.3	91.9	0.744	34.9	— 5.6	1,738	— 7.1	16.3	64
12	106.3	—0.2	91.5	0.742	32.8	—11.2	1,633	—12.6	15.4	63
13	106.1	—0.2	91.1	0.754	33.6	— 9.1	1,672	—10.4	15.8	62
14	105.9	—0.2	90.8	0.731	34.0	— 8.1	1,690	— 9.4	16.0	60
15	105.7	—0.2	90.5	0.732	35.2	— 4.8	1,750	— 6.1	16.5	64
16	105.4	—0.3	90.0	0.688	36.1	— 2.6	1,791	— 3.7	17.0	66
18	105.3	—0.7	89.7	0.644	33.8	—11.4	1,670	—10.1	15.9	70
19	105.0	—0.3	89.2	0.684	35.4	— 4.3	1,751	— 5.6	16.7	68
20	105.0	±0.0	89.2	0.683	32.7	—11.6	1,616	—12.9	15.4	66
21	104.7	—0.3	88.7	0.727	34.2	— 7.5	1,691	— 8.7	16.2	66
22	104.1	—0.6	87.6	0.694	34.2	— 8.8	1,683	— 8.9	16.2	66
23	103.9	—0.2	87.3	0.733	36.5	— 1.5	1,792	— 2.9	17.3	68
25	103.5	—1.2	86.5	0.742	33.9	— 5.6	1,656	—10.1	16.0	64
26	103.7	+0.2	86.9	0.717	34.6	— 6.3	1,696	— 8.0	16.4	68
27	103.5	—0.2	86.5	0.695	35.8	— 3.1	1,754	— 4.8	17.0	72
28	102.9	—0.6	85.4	0.708	33.3	— 9.9	1,624	—11.5	15.8	66
29	102.5	—0.4	84.5	0.740	34.7	— 6.5	1,675	— 8.6	16.3	66
30	102.6	+0.1	84.9	0.743	37.9	+ 1.4	1,845	+ 0.6	18.0	64

TABLE 4.—*Weekly Averages of Daily Basal Heat Production*

Subject: E. S.; height, 150.9 cm.; age, 35 years; normal weight, 55.9 Kg.

	Weight			Heat Production							
Weeks	Kg.	Daily Loss, Kg.	Percentage Over Normal Weight	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate	Thyroid Extract, Gr.
1	79.7	—0.2	42.4	0.693	39.0	+ 5.9	1,640	+ 7.5	20.7	71	...
2	79.1	—0.1	41.4	0.773	35.1	— 5.1	1,472	— 3.6	18.6	69	...
3	79.9	—0.3	42.9	0.762	37.7	+ 1.8	1,583	+ 3.2	19.9	72	...
4	79.6	±0.0	42.5	0.724	34.1	— 7.9	1,432	— 6.6	18.0	69	...
5	78.5	—0.2	40.4	0.723	31.4	—15.2	1,321	—13.5	16.8	62	...
6	77.7	—0.2	39.0	0.723	30.8	—16.9	1,287	—15.2	16.6	59	...
7	77.3	+0.1	38.3	0.750	30.8	—17.2	1,278	—15.9	16.5	60	...
8	76.2	—0.2	36.3	0.755	31.5	—14.9	1,304	—13.1	17.1	58	...
9	75.4	—0.1	34.9	0.765	30.6	—17.5	1,256	—16.0	16.6	56	...
10	75.0	—0.2	34.1	0.751	31.4	—15.2	1,285	—13.5	17.2	53	1.0
11	73.4	—0.2	31.3	0.754	31.7	—13.9	1,281	—13.2	17.5	58	1.0
12	73.1	—0.1	30.7	0.725	32.2	—12.9	1,304	—11.1	18.0	62	1.0
13	72.6	±0.0	29.9	0.762	31.2	—15.8	1,260	—14.1	17.4	57	1.0
14	72.3	±0.0	29.4	0.745	34.2	— 7.5	1,280	— 5.6	19.1	66	2.0
15	71.1	—0.4	27.1	0.841	35.2	— 4.8	1,409	— 2.9	19.9	58	2.0
16	69.7	—0.3	24.6	0.785	35.6	— 3.7	1,416	— 1.5	20.3	72	2.0
17	69.4	+0.1	24.1	0.741	38.0	+ 2.6	1,506	+ 4.9	21.7	70	2.0
Average	....	—0.14	....	.....	33.6	— 9.3	1,377	— 7.7	18.4		

TABLE 5.—*Weekly Averages of Daily Basal Heat Production*

Subject: C. B.; height, 168.9 cm.; age, 23 years; normal weight, 61.4 Kg.

	Weight			Heat Production						
Weeks	Kg.	Daily Loss, Kg.	Percentage Over Normal Weight	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate
1	94.5	−0.4	54.0	0.784	34.2	— 7.4	1,684	— 4.3	17.8	69
2	94.1	−0.1	53.3	0.801	33.6	— 9.2	1,649	— 6.1	17.4	64
3	93.1	−0.1	51.6	0.800	34.1	— 7.9	1,660	— 4.9	17.8	61
4	91.7	−0.3	49.3	0.763	33.6	— 9.3	1,628	— 6.0	17.8	60
5	90.7	−0.5	47.8	0.752	33.1	—10.3	1,598	— 7.3	17.8	58
6	89.7	±0.0	46.1	0.764	36.5	— 1.5	1,750	+ 1.8	19.6	58
7	87.8	−1.0	42.9	0.759	36.4	— 1.6	1,730	+ 1.7	19.8	61
8	87.0	+0.1	41.7	0.777	34.4	— 7.3	1,631	— 2.9	18.8	61
9	85.8	−0.4	39.8	0.771	34.9	— 5.7	1,646	— 1.9	19.2	64
10	85.3	−0.2	39.0	0.787	35.4	— 3.4	1,665	+ 0.6	19.5	57
11	85.4	+0.1	39.1	0.729	35.3	— 4.7	1,659	— 1.0	19.6	56
12	83.8	−0.4	36.6	0.762	34.8	— 6.1	1,596	— 2.3	19.0	60
13	82.9	−0.9	34.3	0.779	37.4	— 0.3	1,736	+ 5.6	21.1	64
14	81.3	−0.2	32.4	0.716	33.2	—10.3	1,536	— 6.0	18.9	56
15	81.0	−0.1	31.9	0.729	32.8	—11.3	1,520	— 6.7	18.8	56
16	80.8	+0.3	31.6	0.739	33.7	— 9.1	1,553	— 4.6	19.3	57
17	79.5	−0.3	29.4	0.728	36.1	— 2.4	1,647	+ 2.0	20.7	59
Average		−0.26	....	.....	34.7	— 6.3	1,640	— 3.2	19.0	

TABLE 6.—*Weekly Averages of Daily Basal Heat Production*

Subject: H. M.; height, 159.4 cm.; age, 21 years; normal weight, 55.5 Kg.

	Weight			Heat Production						
Weeks	Kg.	Daily Loss, Kg.	Percentage Over Normal Weight	R. Q.	Calories per Sq.M. per Hour	Percentage of Deviation from Normal	Calories per 24 Hours	Percentage of Deviation from Normal	Calories per Kg. per 24 Hours	Pulse Rate
1	108.0	−0.2	94.6	0.716	35.7	—3.5	1,787	—5.3	16.6	67
2	106.8	−0.3	92.5	0.711	34.4	—6.9	1,712	—8.6	15.9	66
3	106.0	−0.2	91.0	0.732	34.4	—6.9	1,712	—7.9	16.2	63
4	104.7	−0.3	88.6	0.691	34.7	—7.5	1,701	—8.2	16.3	67
5	103.1	−0.3	85.8	0.724	35.0	—5.0	1,708	—7.1	16.6	67
Average		−0.26	....	.....	34.8	—6.0	1,724	—7.4	16.3	

TABLE 7.—*Insensible Perspiration*

Subject E. S.

			Loss of Weight				Ratio of Heat Production to Insensible Loss
Date	Body Weight, Kg.	Sq. Meter of Body Surface	Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.	Calories per Kg. per Hour	
9/27	80.1	1.75	27	0.34	15.4	0.78	2.30
9/28	79.6	1.75	30	0.38	17.2	0.81	2.13
9/30	80.1	1.75	38	0.48	21.7	....	....
10/11	79.7	1.75	27	0.34	15.4	0.72	2.12
10/ 2	79.7	1.75	25	0.31	14.3	0.79	2.55
10/ 4	79.6	1.75	39	0.49	22.3	0.80	1.64
10/ 5	79.5	1.75	24	0.30	13.7	0.71	2.37
10/ 7	79.2	1.75	43	0.54	24.6	....	....
10/ 8	79.4	1.75	37	0.47	21.2	0.70	1.49
10/10	78.3	1.73	32	0.41	18.5	0.69	1.68
10/11	78.4	1.73	38	0.49	22.0	....	....
10/12	78.3	1.73	42	0.54	24.3	0.72	1.33
10/13	78.4	1.73	22	0.28	12.7	0.68	2.43

TABLE 7.—*Insensible Perspiration—Continued*

Subject: C. B.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight			Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
			Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.		
10/15	78.4	1.73	33	0.42	19.1	0.72	1.71
10/17	77.9	1.73	35	0.45	20.2	0.68	1.51
10/18	77.8	1.73	30	0.39	17.3	0.71	1.82
10/22	77.6	1.72	29	0.37	16.9	0.70	1.89
10/24	77.4	1.72	25	0.32	14.5	0.71	2.22
10/25	77.6	1.72	28	0.36	16.3	0.69	1.92
10/26	77.5	1.72	29	0.37	16.9	0.73	1.97
10/27	76.9	1.72	25	0.33	14.5	0.64	1.94
10/29	76.6	1.71	32	0.42	18.7	0.70	1.67
10/30	76.5	1.71	26	0.34	15.2	0.72	2.12
10/31	75.9	1.71	24	0.32	14.0	0.68	2.13
11/ 1	76.1	1.71	40	0.53	23.4	0.71	1.34
11/ 2	76.3	1.71	30	0.39	17.5	0.71	1.82
11/ 3	75.8	1.71	27	0.36	15.8	0.75	2.08
11/ 4	75.4	1.71	38	0.50	22.2	....	....
11/ 5	75.3	1.71	29	0.39	17.0	0.67	1.72
11/ 6	75.4	1.71	37	0.49	21.6	0.75	1.53
11/ 7	75.6	1.71	27	0.36	15.8	0.68	1.89
11/ 8	75.2	1.71	31	0.41	18.1	0.68	1.66
11/ 9	75.3	1.71	35	0.46	20.5	0.69	1.50
11/12	75.8	1.71	27	0.36	15.8	0.71	1.97
11/15	74.5	1.70	37	0.50	21.8	0.75	1.50
11/19	74.0	1.68	26	0.35	15.5	0.71	2.29
11/23	73.1	1.68	19	0.26	11.3	0.73	2.80
11/27	73.2	1.68	21	0.29	12.5	0.77	2.66
11/30	73.1	1.68	40	0.55	23.8	0.75	1.36
12/ 6	72.4	1.68	30	0.41	17.9	0.68	1.65
12/11	72.4	1.68	41	0.57	24.4	0.78	1.37
12/13	72.5	1.68	42	0.58	25.0	0.83	1.43
12/15	72.3	1.68	26	0.36	15.5	0.84	2.33
12/17	72.2	1.68	21	0.29	12.5	....	....
12/18	72.3	1.68	39	0.54	23.2	....	....
12/24	71.5	1.67	23	0.32	13.8	....	....
Average.....			31	0.41	18.1	0.72	1.89

TABLE 8.—*Insensible Perspiration*

Subject: C. B.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight			Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
			Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.		
6/13	91.5	2.02	22	0.24	10.9	0.73	3.04
6/14	91.6	2.02	28	0.35	13.9	0.71	2.03
6/15	91.8	2.02	31	0.34	15.3	0.73	2.15
6/18	91.5	2.02	29	0.32	14.4	0.80	2.50
6/19	91.1	2.01	26	0.28	12.9	0.77	2.75
6/20	90.7	2.01	32	0.35	15.9	0.73	2.09
6/21	91.0	2.01	18	0.20	9.0	0.68	3.40
6/22	89.7	2.01	36	0.40	17.9	....	....
6/23	89.5	2.01	27	0.30	13.4	0.73	2.43
6/25	89.4	2.01	35	0.39	17.4	0.81	2.08
6/26	89.9	2.01	36	0.40	17.9	0.75	1.88
6/27	90.1	2.01	31	0.34	15.4	0.81	2.38
6/28	90.0	2.01	34	0.38	16.9	0.83	2.19
6/29	89.6	2.00	24	0.27	12.0	0.85	3.15
7/ 2	88.6	1.99	35	0.40	17.6	0.78	1.95
7/ 3	88.7	1.99	39	0.44	19.6	....	....
7/ 4	88.1	1.99	35	0.40	17.6	....	....
7/ 5	87.6	1.98	38	0.43	19.2	0.85	1.98

TABLE 8.—*Insensible Perspiration—Continued*

Subject E. S.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight: Per Hour Gm.	Loss of Weight: Per Kg. per Hour, Gm.	Loss of Weight: Per Sq. Meter per Hour, Gm.	Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
7/ 6	87.1	1.98	22	0.25	11.1	....	....
7/ 7	87.4	1.98	28	0.32	14.2	0.84	2.63
7/ 9	86.6	1.96	33	0.38	16.8	0.79	2.08
7/11	87.0	1.98	31	0.36	15.7	0.72	2.00
7/12	87.5	1.98	34	0.39	17.2	0.76	1.95
7/14	86.2	1.96	31	0.36	15.8	....	....
7/16	86.1	1.96	26	0.30	13.3	....	....
7/19	85.2	1.96	26	0.31	13.3	0.78	2.52
7/20	86.1	1.97	23	0.27	11.7	0.84	3.11
7/22	86.0	1.97	22	0.26	11.2	....	....
7/25	85.1	1.96	19	0.22	9.7	0.92	4.18
7/26	85.4	1.96	25	0.29	12.8	0.77	2.66
7/27	85.3	1.96	21	0.25	10.7	0.79	3.16
7/28	85.1	1.96	29	0.34	14.8	0.80	2.36
7/29	85.0	1.96	23	0.27	11.7	....	....
7/30	85.5	1.96	23	0.27	11.7	0.82	3.04
7/31	85.2	1.96	19	0.22	9.7	0.81	3.68
8/ 1	85.6	1.96	25	0.29	12.8	...	....
8/18	83.6	1.94	25	0.30	12.9	0.86	2.87
8/19	83.6	1.94	28	0.34	14.4	....	....
8/20	83.1	1.93	35	0.42	18.1	0.94	2.24
8/22	81.8	1.92	27	0.33	14.1	0.81	2.46
8/23	82.3	1.92	25	0.30	13.0	....	....
8/25	81.7	1.92	37	0.45	19.3	....	....
8/26	81.7	1.92	30	0.37	15.7	....	....
8/27	81.0	1.92	26	0.32	13.5	0.72	2.25
8/28	81.8	1.92	29	0.35	15.1	0.93	2.66
8/29	81.7	1.92	24	0.29	12.5	....	....
8/30	81.4	1.92	16	0.20	8.3	....	....
8/31	81.3	1.92	28	0.34	14.6	0.73	2.15
9/ 1	81.0	1.92	38	0.47	19.8	0.77	1.64
9/ 2	81.2	1.92	26	0.32	13.5	....	....
9/ 3	81.1	1.92	27	0.33	14.1	....	....
9/ 4	81.1	1.92	25	0.31	13.0	0.77	2.49
9/ 5	81.0	1.91	30	0.37	15.7	0.80	2.16
9/ 6	80.8	1.91	37	0.46	19.4	0.78	1.70
9/13	80.4	1.91	37	0.46	19.4	0.81	1.76
9/20	79.2	1.90	25	0.32	13.2	0.91	2.85
9/22	79.7	1.90	34	0.43	17.9	0.89	2.07
Average			29	0.33	14.5	0.80	2.92

TABLE 9.—*Ratio of Heat Production per Hour to Insensible Perspiration per Hour (Benedict-Root Table Recalculated)*

Insensible Perspiration, Gm.	Heat Produced per 24 Hours, Calories	Ratio of Heat Produced to Insensible Perspiration	Insensible Perspiration, Gm.	Heat Produced per 24 Hours, Calories	Ratio of Heat Produced to Insensible Perspiration
14	900	2.68	38	1,655	1.76
16	965	2.51	40	1,715	1.79
18	1,028	2.38	42	1,775	1.76
20	1,090	2.27	44	1,840	1.74
22	1,155	2.19	46	1,900	1.72
24	1,215	2.11	48	1,965	1.71
26	1,280	2.05	50	2,025	1.69
28	1,345	2.00	52	2,085	1.67
30	1,405	1.95	54	2,145	1.66
32	1,470	1.92	56	2,210	1.64
34	1,530	1.88	58	2,275	1.63
36	1,590	1.84			

COMMENT

The daily basal metabolism of all three subjects, as given in tables 1 to 3, fluctuated considerably, varying from 1,751 to 1,163 calories per twenty-four hours in E. S., from 1,876 to 1,392 calories in C. B. and from 1,880 to 1,616 calories in H. M. However, the weekly averages given in tables 4 to 6 show that as the weight of the subjects slowly decreased, there was also a gradual decrease in the heat production. This was less marked in C. B., who was more neurotic than the other two subjects. The high value of her last weekly average was due in part to the fact that she was restless and anxious to leave the hospital. On the basis of the averages of the first week and those of the next to the last week, her basal metabolism decreased from 1,684 to 1,553 calories per twenty-four hours as her body weight was reduced from 94.5 to 81 kilograms. In other words, a reduction of 16.7 per cent of body weight was accompanied by a decrease of 8.4 per cent in basal metabolism. The heat production of E. S. decreased steadily from a weekly average of 1,640 calories per twenty-four hours to that of 1,256, which was 17.5 per cent below her normal standard according to DuBois and 16 per cent below as compared with Benedict's standard. She was therefore given treatment with thyroid extract, first 1 and then 2 grains (0.06 and 0.13 Gm.) a day. In spite of the administration of thyroid extract, her basal metabolism decreased from 1,640 to 1,416 calories per twenty-four hours as her weight was reduced from 79.7 to 69.7 kilograms, using also the averages of the first week and those of the next to the last week of the experiment. The decrease in heat production in this subject exceeded that of her body weight. A reduction of weight of 14.3 per cent was followed by a lowering of 15.8 per cent in basal metabolism. Unfortunately, our best subject, H. M., who was calm and willing to cooperate, had to go home after taking part in the experiment for five weeks. In spite of the short duration of the experiment, she lost 4.9 kilograms, or 4.8 per cent of her initial weight. Her loss of weight was followed by a decrease of 4.6 per cent in basal metabolism, from a weekly average of 1,787 to that of 1,708 calories per twenty-four hours.

In the case of C. B., the diminution of body weight was accompanied by an increase in heat production when the latter was expressed as calories per kilogram per twenty-four hours. Thus, as the weight decreased from 95 to 79.7 kilograms, the basal metabolism increased from 17.4 to 21.4 calories per kilogram per twenty-four hours. No similar relationship was observed in the results of the other two subjects. Their heat production expressed as calories per kilogram of body weight fluctuated irrespective of the loss of weight. When the values of the weekly averages were used, the coefficient of correlation

between the body weight in kilograms and the calories per kilogram per twenty-four hours was —0.71 for C. B., —0.33 and —0.25 for E. S. and H. M., respectively, showing a fair degree of inverse correlation in C. B. and only a slight correlation in the other two.

In comparing our results with normal standards using the actual weight of the patients, the basal metabolism of all three subjects was lower than either the Benedict or the DuBois standard. The average values were 9.3, 6.3 and 6.0 per cent below the Dubois standard or 7.7, 3.2 and 7.4 per cent below Benedict's. It is of interest to observe that with no exception in the case of C. B. and with a few exceptions in E. S., the values of heat production were closer to the Benedict standard than to the DuBois. On the other hand, the reverse was true in the case of H. M., who was far more obese than the other two. If the ideal weight of the subjects was used, the heat production of all three became higher than their standard. Thus, for instance, at the beginning of the experiment the heat production (using weekly averages) of E. S. was 25.6 per cent above the Benedict standard and at the end of the experiment, 15.3 per cent above. The corresponding values for C. B. and H. M. were 16.3, 13.8, 28.9 and 32.2, respectively. These values are in close agreement with those reported by Strang and Evans,[2] who pointed out that, using ideal weight, obese subjects invariably showed an increased basal metabolism which decreased with the reduction of body weight. Since the experimental diet was adequate in all food essentials except caloric value, which was lowered by reducing chiefly the fat content to a minimum, the decrease of body weight of these subjects must be due largely to the loss of adipose tissue. The reduction of their energy production is, therefore, probably the result of the biologic adaptation of the body to a lowered energy intake as was pointed out by Lusk.[3]

The influence of the reduction of body weight on the respiratory quotient varied with the subjects. There was a tendency toward a gradual decrease during the course of reducing weight in the case of C. B. The weekly averages of the first three weeks gave a value close to 0.8 which gradually decreased to a figure near 0.7 at the end of the experiment. The respiratory quotient of H. M. was unusually constant; the weekly averages varied from 0.691 to 0.732. In the case of E. S., the values fluctuated independently of body weight between 0.841 and 0.693.

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2. Strang, J. M., and Evans, F. A.: The Energy Exchange in Obesity, J. Clin. Investigation **6**:277 (Oct.) 1928. Evans, F. A., and Strang, J. M.: A Departure from the Usual Methods in Treating Obesity, Am. J. M. Sc. **177**:339 (March) 1929.

3. Lusk, G.: The Physiological Effect of Undernutrition, Physiol. Rev. **1**:523 (Oct.) 1921.

The pulse rate of E. S. showed a tendency to vary with the basal heat production. The weekly averages ranged between 53 and 72. No relation between the pulse rate and the metabolism was found in the other two subjects. The pulse rate of C. B. varied from 54 to 72, with the majority lying between 55 and 65. The values for H. M. were exceptionally constant; the weekly averages ranged between 63 and 67.

During the experimental period the study of insensible perspiration was also conducted on two of the three subjects. The measurements were made during a ten hour period at night from 9:45 p. m. to 7:45 a. m., a platform scale being used, the so-called "silk scale" recommended by Benedict.[4] Tables 7 and 8 show that the values varied widely in both subjects; in E. S. they ranged from 0.58 to 0.26, with an average of 0.41 Gm. per kilogram per hour. When computed on the basis of a square meter of body surface, they ran between 25 and 12.5, with an average of 18.1 Gm. per square meter per hour. The corresponding values for C. B. were 0.47 and 0.20, with an average of 0.33 Gm. per kilogram per hour and the values per square meter per hour were from 19.8 to 8.3, with an average of 14.5 Gm. The average insensible loss per hour of these two subjects was 31 and 29 Gm., which is in close agreement with the results reported by previous investigators on normal subjects. The average insensible perspiration per person reported by Benedict and Hendry[5] from a study of a group of girls between the ages of 12 and 17 was found to be about 30 Gm. per hour, with the exception of two cases in which it was 38 and 45. In a later investigation[6] made on two groups of girls, the same authors gave the average value as 33 Gm. per hour. In a study[4] made on a woman weighing 60 kilograms, during the greater part of a year, Benedict and Root gave the average as 28.7 Gm. per hour. In the same report the authors also gave 24 Gm. per hour as the average insensible loss of a woman studied in a series of organized weighings with the platform scale.

In order to facilitate the comparison of basal heat production with the insensible loss, the ratio of the two was computed as is shown in tables 7 and 8. In each case, the basal metabolism was taken within an hour following the morning weighing. In E. S., the ratio varied from 2.8 to 1.33, with an average of 1.89. The corresponding values for C. B. were 4.18, 1.64 and 2.92. Since the latter subject is more

4. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38:1** (July) 1926.

5. Benedict, F. G., and Hendry, M. F.: The Energy Requirements of Girls from Twelve to Seventeen Years of Age, Boston M. & S. J. **184:**217 (March 3) 1921.

6. Benedict, F. G.: The Basal Metabolism of Young Girls, Boston M. & S. J. **188:**127 (Feb. 1) 1923.

excitable, a greater variation in the results would be expected. In comparison with the curve of the relationship between insensible perspiration per hour and the heat production per twenty-four hours constructed by Benedict and Root,[4] our values do not agree closely with theirs. In the case of E. S., the insensible loss is usually higher than the predicted value, whereas the reverse is true of C. B.

Table 9 shows that, according to Benedict's prediction, the higher the basal metabolism is, the lower the ratio. Thus, by recomputing his table 4,[4] as the basal metabolism ran from 900 to 2,272 calories per twenty-four hours, the ratio decreased from 2.68 to 1.63. The values of our two subjects failed to correspond with the foregoing prediction. E. S. had an average basal metabolism of 1,377 calories per twenty-four hours; the average ratio was 1.89, whereas C. B. had a higher basal, 1,640 calories per twenty-four hours, with a higher ratio of 2.92. We are unable to explain whether this discrepancy is due to the extra adipose tissues of our subjects or to some other biologic factors.

SUMMARY

1. A total of 190 metabolic tests were made during a period of reducing weight by diet in three obese women, one of whom had diabetes. In the latter a steady decrease in basal metabolism was observed until thyroid extract was administered. In the other two subjects, the decrease was less marked.

2. Per kilogram of body weight, the basal metabolism of one of the subjects, C. B., increased gradually with the loss of weight, but no such relationship was observed in the other two. The coefficient of correlation between the loss of body weight and the increase of heat production per kilogram per twenty-four hours showed a fair degree of inverse correlation, —0.71 in C. B. and only a very slight correlation in the other two, —0.33 and —0.25, respectively.

3. A slight tendency toward the lowering of the respiratory quotient was observed in C. B., but not in the others.

4. In E. S., the pulse rate showed a tendency to decrease with the basal metabolism, but the values varied independently of the basal metabolism in the other two subjects.

5. Insensible perspiration of two of the subjects showed marked fluctuation. The average insensible loss was 31 Gm. per hour in E. S. and 29 Gm. in C. B. No definite relationship was found between insensible perspiration and basal metabolism in these two subjects.

THE ORIGIN OF UROBILINOGEN

A CLINICAL EXPERIMENT *

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From time to time physiologists devise various experimental procedures to test their theories. Occasionally, however, one may meet with a clinical condition that corresponds to the ideal laboratory experiment for explaining a given phenomenon. The literature contains many such examples, and the case reported here is an additional demonstration. Its data are of interest particularly with regard to the origin of urobilinogen in the body.

Estimation of the urobilinogen content of urine has now been a routine in this laboratory for a number of years, particularly in the study of disorders of the blood and liver. All methods available have been tried, but from a quantitative point of view none has been found perfect. For practical purposes, however, the method described by Wallace and Diamond in 1925, has been found to be the most satisfactory and has been in use since it was first reported. As in all laboratory tests with a large routine and accumulation of data, anomalous results are met with. Provided technical errors have been eliminated, the interpretation of such results never fails to be of interest. They may alter the interpretation of future data and occasionally contribute to the knowledge of physiology.

Unless one is certain of the facts of an experiment and unless the results are definite, one should hesitate to publish data that might add to the confusion now existing with regard to the various functions of the liver. Mann put it very well when he stated that "the liver has served as the waste-basket of the body into which have been dumped numerous manuscripts of conjecture concerning obscure physiological and pathological phenomena and uncounted prescriptions." In the case to be reported, the experimental results were, however, sufficiently definite to warrant their publication.

It is not my purpose to review this subject in this brief report, as excellent reviews are now available in the literature. A few observations must, however, be made in order to separate theories from facts and also because they are essential for the interpretation of the data obtained.

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* Submitted for publication, May 17, 1930.

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There is general agreement that hemoglobin, bilirubin and urobilinogen are intimately related. Not only is there similarity between their chemical structures, but there is also experimental evidence: It has repeatedly been shown that urobilinogen may be produced, in vitro, by reduction of bilirubin with sodium amalgam or other reducing agents.

Whether bilirubin has its origin in the hemoglobin of the blood only or whether it is derived from other sources as well is still unsettled. No one, however, doubts that bilirubin can, and does, originate from hemoglobin. There may also be some doubt as to the relative importance of the different sites of bile formation (liver, bone-marrow, etc.). There appears, however, to be sufficient agreement that the liver can, and does, supply this function. The biliary passages are also the chief paths of elimination of these pigments, and by means of them the latter pass into the intestinal tract. With regard to the course of events beyond this stage, however, the subject is much more controversial.

There appears to be general agreement that in the intestine, because of the reducing properties of its flora, bilirubin is converted into urobilinogen. The urobilinogen may then follow one of three paths. It may be excreted with the feces or reabsorbed into the liver or into the circulation and eliminated in the urine. The amounts found in the urine are small, under normal conditions. Excessive quantities are found either in association with hepatitis or in conditions associated with excessive destruction of blood. Provided the liver is not exposed to organisms with reducing properties, it is generally accepted that extra-intestinal reduction of bilirubin to urobilinogen does not take place. Recently, Wallace and Diamond, following a review of this subject and some experimental work, again concluded that there is no extra-enterogenous formation of urobilinogen. The following case, however, is presented as evidence to the contrary. Though the experiment was clinical, the results, as I have stated, appear to have been so definite as to warrant their consideration. The data demonstrate not only the possibility of an extra-intestinal origin of urobilinogen, but also that the formation of this pigment from bilirubin may take place in the absence of its exposure to bacteria with reducing properties. The following are the relevant facts:

REPORT OF A CASE

A woman, aged 44, was admitted into the gynecological service of the Montreal General Hospital on March 16, 1930, with acute abdominal pain. The diagnosis was not definite, but the probabilities considered were (*a*) an ovarian cyst with torsion of the pedicle and (*b*) a malignant growth terminating in some form of abdominal crisis. As this report is essentially biochemical, no further observations are relevant with regard to the clinical aspects of the case. The laboratory observations of special interest here were as follows: urobilinogen was present in the urine in a dilution greater than 1:1,000; the van den Bergh reaction was negative.

The association of such large amounts of urobilinogen in the urine with normal quantities of bilirubin in the blood was never met with before in my experience. To exclude technical errors, the test was repeated on the afternoon of the same day; the results were the same.

In view of these observations and the prevalent conception of the physiology of bile pigment, I suggested that there was probably some extravascular accumulation of blood; and that this blood was being reduced to urobilinogen at its source. The latter suggestion appeared reasonable, since if the reduction was taking place in the intestines, it would imply that large amounts of bilirubin had to enter the circulation from the extravascular collection of blood. If this was the case, the plasma had to contain either free hemoglobin or excess bilirubin. There was no evidence of hemolysis, and the van den Bergh reaction was negative.

Though it is known that bilirubin may be reduced to urobilinogen by nonbacterial agents in vitro (sodium amalgam, etc.), as far as I could ascertain from the literature, bacterial reduction is the only type that has ever been reported in the body. It was therefore also suggested that this extravascular accumulation of blood was infected.

In making the foregoing suggestions, it was assumed that the van den Bergh reaction is specific for bilirubin and that the para-dimethyl-amido-benzaldehyde reagent used is specific for urobilinogen. As a matter of fact, the latter assumption is not correct, since the reaction is common to pyrrol groups. In view, however, of the large experience with this reagent, it may reasonably be assumed that the red color obtained when this reagent is added to urine is practically wholly due to urobilinogen.

On March 20, a laparotomy was performed and the preoperative diagnosis was proved to be partly correct. The condition was found to be a large ovarian cyst with torsion of the pedicle. The surface was very dark and obviously cyanotic. On opening the cyst it was found full of blood, a specimen of which was obtained for bacteriologic examination. The report from the pathologist showed that the blood was sterile.

That the mass of blood in the cyst was the source of the excessive amount of urobilinogen found in the urine appears obvious from the fact that in a specimen of urine obtained twelve hours after operation, that is, after the removal of the mass of extravascular blood, the quantity of urobilinogen was normal, namely, less than in 1 : 10 dilution. In this case, we therefore appear to have proof that urobilinogen can be formed not only outside of the intestinal tract but also in the absence of bacteria with reducing properties. An explanation for the development of the urobilinogen in the cyst is suggested.

Since the blood in the cyst was bathed with other body fluids, and since the latter contained oxygen in solution, one would hardly expect reduction of hemoglobin, in view of the marked avidity of the latter for oxygen. With the twisted pedicle, however, three conditions would immediately result, namely: (*a*) anoxemia, (*b*) accumulation of carbon dioxide and (*c*) because of the anoxemia, accumulation of lactic acid. According to hemoglobin dissociation curves, the increase of carbon dioxide tension and hydrogen ion concentration would lessen the avidity

of hemoglobin for oxygen; with progressive reduction, hemoglobin would be converted into bilirubin and then into urobilinogen.

The foregoing explanation is only a suggestion. The purpose of this report is to record a clinical experiment which appears to demonstrate that urobilinogen may not only be formed in the body outside of the intestinal tract, but also in the absence of bacteria as reducing agents.

THE CORRELATION OF WIDAL'S POSTDIGESTIVE LEUKOPENIA AS A TEST FOR LIVER FUNCTION WITH THE NORMAL RHYTHM OF THE LEUKOCYTES *

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Widal, Abrami and Iancovesco [1] described a test for liver dysfunction which they believe is based on an anaphylactic blood reaction. This reaction, to which they gave the name of hemoclastic crisis, manifests itself as (*a*) leukopenia with a relative lymphocytosis, (*b*) fall of blood pressure, (*c*) decrease in the refractometric index of the serum and (*d*) an increase in the coagulation time of the blood. The authors stated that these phenomena are a response of the presence of low proteins (peptones) in the general circulation. Their theory for the appearance of these products in the general circulation is that during digestion of protein the partially digested proteins which reach the liver via the portal circulation pass through and enter the general circulation when the liver is diseased. The normal liver prevents this transmission, because it has the property of arresting the low proteins (proteopexic function).

These authors offered the following animal experimentation in support of their theory. During digestion of protein either shunting of the portal blood into the systemic circulation by Eck's fistula or the injection of portal blood into a systemic vessel provoked hemoclastic crisis. The authors stated that the leukocyte test for hemoclastic crisis is delicate and definite, and that it will detect liver dysfunction with small quantities of protein. The technic of this test as described by Widal and his collaborators is as follows: The patient fasts for at least five hours preceding the test. A single control white cell count

* Submitted for publication, Feb. 14, 1930.

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* The tests for liver function were carried out by Dr. Norman Jolliffe as a part of his study of liver function (J. Clin. Investigation **8**:419 [April] 1929).

1. Widal, F.; Abrami, P., and Iancovesco, N.: L'épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, Presse méd. **28**:893 (Dec. 11) 1920.

is made, and immediately 200 cc. of milk is given by mouth. White blood cell counts are repeated every twenty minutes for two hours. In the presence of liver dysfunction, leukopenia develops, usually within the first hour, the maximum of which is reached in the first twenty to forty minutes. At the end of ninety minutes, the count returns to the control level or goes above it. When the liver is intact, the counts do not fall below the initial count, and a leukocytosis may follow (digestive leukocytosis).

The authors obtained a positive reaction in thirty-eight of thirty-nine patients with disease of the liver. The test gave negative results in all of eleven normal persons, in nine of whom leukocytosis appeared. The test gave negative results in other pathologic conditions in which the liver was intact.

REVIEW OF THE LITERATURE

The literature, which is largely European, is divided in its criticism of the work. The value of the test and its theoretical basis are both disputed. Shaw [2] applied the test to seven patients with disease of the liver, and to twenty-three normal persons. He controlled his results by making serial counts while the patient was at rest, and by giving substances other than milk—distilled water, casein and butter fat. His conclusions were: 1. The leukocyte count under normal conditions fluctuates considerably, but at times it is in equilibrium. 2. There is no digestion leukocytosis or "digestion leukopenia," and the results recorded as such in the literature on hemoclasis are simply an expression of the phase of the normal curve at the time the test is done.

The author quoted Mauriac and Cabouat,[3] Servantie, Panzat and Monod [4] and Kobryner [5] to support his observations of variations in the leukocytes in normal subjects at rest.

Storm van Leeuwen, Bien and Varekamp [6] obtained a fall in leukocytes in normal and in asthmatic persons within two minutes after the ingestion of a meal. They showed that the curves varied in the same subjects when the counts were repeated. They concluded that the leukocyte curve does not give evidence of a "crise hémoclasique."

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2. Shaw, A. F. Bernard: A Study of the Haemoclastic Crisis Test for Liver Function, With Special Reference to the Leucocytic Changes, Brit. M. J. **1**:914 (May 16) 1925.

3. Mauriac, P., and Cabouat, P.: Paris méd. **11**:407, 1921.

4. Servantie; Panzat and Monod: J. de méd. de Bordeaux **12**:360, 1921.

5. Kobryner, A.: Compt. rend. Soc. de biol. **90**:1475, 1924.

6. Storm van Leeuwen, W.; Bien, Z., and Varekamp, H.: On Alimentary Leucocytosis in Its Relation to the Crise Hémoclasique of Widal, J. Exper. Med. **36**:414, 1922.

Middleton and Thewlis,[7] in a study of patients with catarrhal cholangeitis, concluded that the protein factor was not essential for the production of hemoclastic shock. Feinblatt,[8] in a study of eighty normal persons, found a consistent leukocytosis after the ingestion of milk. Of fifty patients with various diseases, he obtained a positive reaction in twenty-two.[9] He concluded that a positive Widal reaction is indicative of faulty hepatic proteopexic function, and that the test is not a measure of the quantitative gross lesion.[10]

Brown [11] accepted the test as probably yielding information respecting special functions of the liver, but he drew no conclusions from his own observations on patients with questionable disease of the liver.

Sabin, Cunnningham, Doan and Kindwall [12] showed that regardless of digestion, the leukocytes had a normal physiologic rhythm which was approximately hourly. At every hourly period the leukocyte count reached a peak which was followed by a depression of varying depth. At times the fall in the number of leukocytes reached 50 per cent of the preceding peak. This rhythmic curve ascended through the day to the afternoon, so that the high counts of the afternoon doubled the low counts of the morning.

Mention has already been made of other workers who have recognized a normal variation in the leukocytes.[13] Shaw,[14] working independently, was able to confirm the work of Sabin and her co-workers, and showed also that there was a diurnal variation in the leukocytes. Doan and Zerfas [15] showed that comparable leukocyte

7. Middleton, W. S., and Thewlis, Ethel: The Leukocytic Phase of Haemoclastic Shock, J. Lab. & Clin. Med. **10**:462, 1924 and 1925.

8. Feinblatt, Henry M.: Alimentary Leukocytosis in Eighty Normal Men: A Study in Reference to the Crise Hémoclasique of Widal, J. A. M. A. **80**:613 (March 3) 1923.

9. Feinblatt, Henry M.: Alimentary Leukocytosis in Various Pathologic Conditions: A Further Study in Reference to the Crise Hémoclasique of Widal, Arch. Int. Med. **33**:210 (Feb.) 1924.

10. Feinblatt (footnotes 8 and 9).

11. Brown, Thomas: Notes on Hemoclastic Shock as a Test of Liver Function, Ann. Clin. Med. **1**:89 (Sept.) 1922.

12. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: The Normal Rhythm of the White Blood Cells, Bull. Johns Hopkins Hosp. **37**:14, 1925.

13. Shaw (footnote 2). Mauriac and Cabouat (footnote 3). Servantie, Panzat and Monod (footnote 4).

14. Shaw, A. F. B.: The Diurnal Tides of the Leucocytes of Man, J. Path. & Bact. **33**:1, 1927.

15. Doan, C. A., and Zerfas, Leon G.: The Rhythmic Range of the White Blood Cells in Human Pathological Leucopenic and Leucocytic States with a Study of Thirty-Two Human Bone Marrows, J. Exper. Med. **46**:511, 1927.

rhythms occur in many types of disease. Smith and McDowell [16] found the rhythm unaffected during menstruation, mild fatigue and moderate exercise.

If this rhythmic variation is accepted as a normal physiologic process of the leukocytes, then Widal's leukocyte test for liver function becomes untenable. To be of any value, the control counts must extend over a period sufficiently long to portray the physiologic rhythm of the leukocytes, and to interpret a positive reaction, either the entire rhythmic curve of the leukocytes must be depressed, or, if the interpretation is to depend on the results in the sixty minutes succeeding the ingestion of milk, the depression must exceed the physiologic depression. It seemed, therefore, that additional information to the subject could be made if in a series of patients with disease of the liver, Widal's leukocyte test for liver dysfunction was correlated with the work of Sabin and her collaborators.

REPORT OF STUDY

The study was made on twenty hospital patients. Ten had heart disease; in eight of these there was congestive failure with enlarged livers, and in two the hearts were well compensated and served as controls. Four were patients with acute catarrhal jaundice; one patient showed extensive primary carcinoma of the liver, later proved by autopsy; one was a patient with carcinoma of the stomach who probably had extensive liver metastasis; one patient had jaundice following the administration of arsphenamine; one patient had an amebic abscess of the liver which was drained by repeated aspiration with apparent cure; one patient had cirrhosis of the liver; and one patient with a parkinsonian syndrome was used as a control. Evidence of disease of the liver was determined by the clinical study and by the results of four tests for liver function carried out on each patient. These were: the levulose tolerance test, the bromsulphalein test, a daily determination of the urinary urobilinogen according to the technic of Wallace and Diamond [17] and quantitative determinations of serum bilirubin (van den Bergh). The results of these tests are shown in the accompanying table.

All of the patients studied showed some form of abnormality of the liver except those who served as controls (5, 7 and 19). In only one patient (11) were we unable to palpate the liver. In each patient, at least one of the four tests for liver function showed a deviation from the normal. The serum bilirubin (the quantitative test of van den

16. Smith, Christiana: and McDowell, Anna Mary: Normal Rhythm of White Blood Cells in Women, Arch. Int. Med. **43**:68 (Jan.) 1929.

17. Wallace, George B., and Diamond, Joseph S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

Bergh) was increased in all patients. The bromsulphalein test showed a retention in twelve of the seventeen, the output of urinary urobilinogen was increased over the normal in nine, and the levulose tolerance was impaired in six. In fifteen patients the tests were positive in combinations, no two of which were always together. In only two patients (13 and 15) was the van den Bergh reaction alone positive. On two patients with cardiac disease who had congestive heart failure (13 and 17) and on one patient (14) who had acute catarrhal jaundice, the study was repeated after there was marked clinical improvement. The results of

Results of Correlation Between Widal's Leukocyte Test and That of Sabin, in a Series of Twenty Patients with Disease of the Liver

Case	Diagnosis	Jaundice	Liver, Cm. from Xiphoid	Bromsulphalein, per Cent	Serum Bilirubin, Mg. per Cent	Urobilinogen Dilu. + 1 in.:—	Levulose Tolerance			
							Fasting	30	60	120
1	Carcinoma of liver	+	20	15	3.8	160	69	84	82	100
2	Cardiac	0	8	5	0.92	128	92	120	135	133
3	Carcinoma of stomach	0	7	5	0.51	40	77	98	100	96
4	Acute jaundice	++	4	35	12.5	20	93	119	137	105
5	Cardiac	0	0	0	<0.5	4	78	92	106	81
6	Cardiac	0	10	15	1.1	32	82	96	103	105
7	Parkinsonian syndrome	0	0	0	<0.5	8	100	125	125	100
8	Cardiac	+	13	5	4.3	64	108	125	130	127
9	Cardiac	0	10	5	0.17	128	100	114	117	110
10	Cardiac	0	16	5	0.63	15	108	125	137	125
11	Acute jaundice	++	0	0	3.0	80	62	66	80	91
12	Cirrhosis of liver	0	18	0	0.94	32	97	116	146	144
13a	Cardiac	0	15	0	1.8	16	78	82	95	105
13b		0	8	0	<0.5	2	72	82	90	100
14a	Acute jaundice	++	12	20	10.1	20	77	88	109	83
14b		0	0	0	<0.5	40	101	105	118	100
15	Abscess of liver	0	8	0	1.1	4	100	100	102	109
16	Cardiac	0	11	15	0.94	16	70	95	100	102
17a	Cardiac	0	12	0	0.64	8	100	135	181	210
17b		0	5	0	<0.5	4	117	122	128	114
18	Jaundice following the use of arsphenamine	++++	7	10	9.0	512	137	150	155	166
19	Cardiac	0	0	0	<0.5	4	80	95	94	81
20	Acute jaundice	++	4	5	3.8	16	83	80	117	79

the second series of tests are given in the table in spaces 13-*b*, 17-*b* and 14-*b*. In each of these instances, a test previously positive became negative. In the case of 14-*b*, a single specimen of urine gave a positive reaction for urobilinogen in a dilution of 1:40, despite the fact that numerous specimens both at the height of the disease and subsequently were always negative when dilutions of more than 1:20 were used. The latter three patients served as controls, both for themselves and for the entire group.

On the basis of these tests and the observations made clinically and at autopsy, it was assumed that all of the patients except the ones used as controls had abnormalities of the liver, either structural or functional or both. It was felt, therefore, that this was a group of patients on whom the value of Widal's leukocyte test for liver function could be studied.

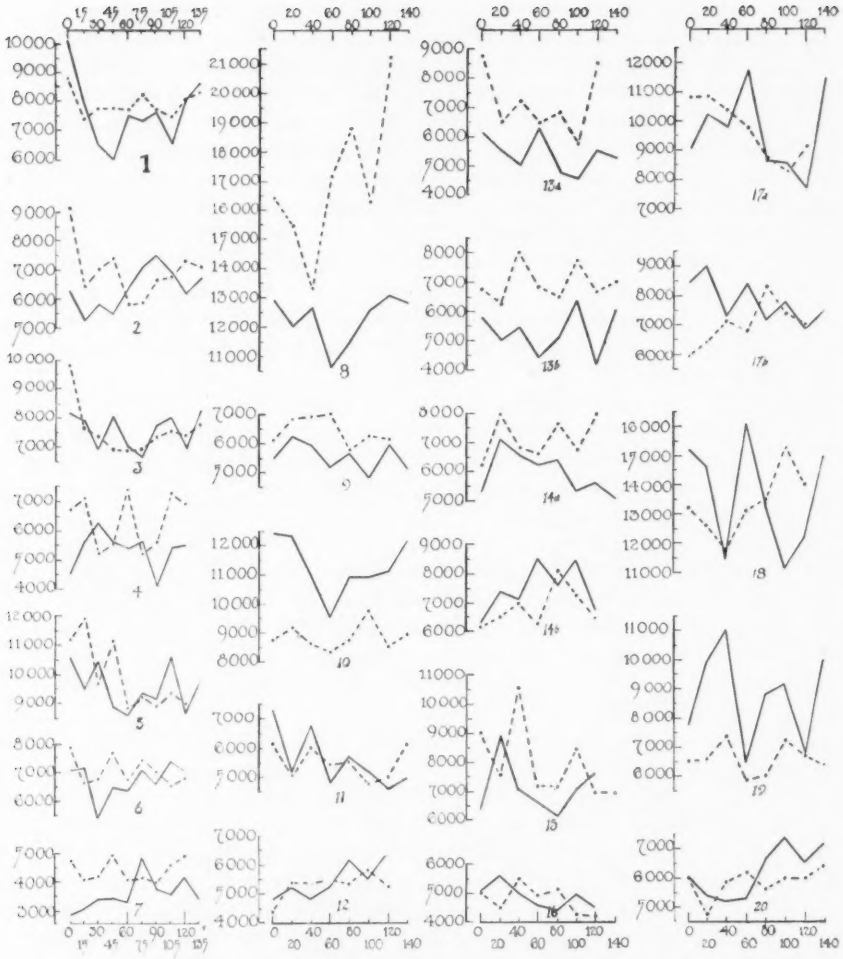
The method was to make counts of the total white blood cells at either fifteen or twenty minute intervals for a period of two hours or more. Two series of counts, a control and test series, were done on each patient. Usually these counts were done on consecutive mornings; in a few instances, they were done on consecutive afternoons. When the counts were done in the morning, the patient omitted his breakfast. In those instances in which the study was made in the afternoon, the patient had been without food or drink for at least five hours. The control series of counts was done while the patient was fasting; the test series was done under the same conditions, except that the patient was given 200 cc. of milk by mouth immediately after blood was withdrawn for the first or key count. The same pipet and counting chamber were used for all observations, and an automatic lancet was used to puncture the skin. The blood was drawn from the finger tips, and a different finger was used for each count. Duplicate counts were done and the average of the two taken. All of the counts were done by the same observer.

The counts are plotted in curves in the accompanying chart. Inspection of the chart shows at once that extensive fluctuations occur in both the control and the test curves. They are not long enough to show any definite rhythm, but in a general way they show depressions and ascents rather than a tendency toward a horizontal straight line.

A study of all the control curves shows that there is at least one period in each curve, except that of patient 12, in which there is a peak and a subsequent fall. Each of these depressions in the curves might have been interpreted as a positive Widal reaction had a test meal been given immediately following the peak count. The control curves show, therefore, that Widal's leukocyte test as it is described by the authors cannot be used to determine liver function.

The second phase of the problem was to determine whether the test meal depressed the entire rhythmic curve and whether such depression could be interpreted as a positive Widal reaction. In only four of twenty-three test curves (1, 11, 16, 17-*b*) might such a deduction be made. On the other hand, in as many of the control series of curves (2, 3, 5, 17-*a*) the same downward tendency existed. There is no evidence, therefore, that the meal depressed the entire curve during the period studied. If such a depression exists beyond the two hour period, this fact does not lend support to the criteria set down by Widal and his collaborators that after ninety minutes the white blood count comes back to the control level or goes above it.

The third phase of the study was to determine whether the ingestion of the test meal was followed by an immediate fall in the number of white blood cells which was greater than the greatest fall that occurred anywhere in the control curves. It is clear that the initial fall succeeding



Curves showing total white blood cell counts for twenty subjects. The abscissas represent time in minutes; the ordinates represent the number of leukocytes. In each case the value of the ordinates is given to the left of the curve. The broken line is the control curve; the solid line, the test curve.

the test meal must be compared, not with the initial fall of the control curve, but with the greatest fall in that curve. Such comparison shows that in only seven of the twenty-three instances (1, 6, 10, 11, 13-*b*, 18, 20) did the depression succeeding the test meal exceed the greatest depression in the control. The number is less than one third of the total number of curves and is what might be anticipated if the test meal does not affect the number of leukocytes. If comparison is made between the greatest depression in test curve, regardless of its relationship to the antecedent test meal, with the greatest depression in the control curve, then in thirteen sets of curves (1, 6, 10, 11, 13-*b*, 18, 20, 4, 7, 14-*a*, 17-*a*, 17-*b*, 19) the greatest depression occurs in the test curve; in the other ten sets, the greatest depression appears in the control curves. The numbers are sufficiently close to indicate that the control and test curves are similar.

Further evidence that the two curves are similar is evinced when one considers the number of depressions that might be interpreted as positive Widal reactions were test meals given at the preceding peak count. Such consideration shows that there are a total of thirty-two depressions in all of the control curves and thirty in the test curves.

SUMMARY AND CONCLUSION

Serial counts of the total number of leukocytes were made every fifteen or twenty minutes for two hours on seventeen patients who showed evidences of liver dysfunction. These determinations were made according to the technic outlined by Widal for determining such dysfunction. A control series of counts was made under the same conditions, except that the test meal was omitted. Marked fluctuations occurred in the total number of leukocytes from period to period in both series of curves. There was no evidence that the ingestion of milk had any effect on the number of white blood cells in the peripheral circulation during a two hour period. From this study no evidence can be adduced that Widal's leukocyte test for hemoclastic crisis is a test for liver function.

SPHENOPALATINE PHENOMENA

PRESENT STATUS OF KNOWLEDGE *

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IN COLLABORATION WITH
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DETROIT

Our object in this paper is to bring together the more important observations that have accumulated in the literature on the sphenopalatine ganglion during the past twenty-five years and the more important observations that have been made during eight years of original work on this subject. The original work includes more than 2,000 cases and more than 10,000 instances, counting multiples and repetitions, of remote dysfunctions [1] being arrested by anesthetizing the sphenopalatine ganglions. This should provide a working guide that will bring the student of the subject to the front lines of advance without unnecessary delay.

Anesthetization of the sphenopalatine ganglions and the injection of alcohol into them have one feature in common: They render the ganglions impervious to the passage of nerve currents. An injection may be considered the equivalent of an anesthetization lasting several months instead of several hours, and so the associate phenomena need not be discussed separately.

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* Submitted for publication, May 25, 1930.

* From the Jefferson Clinic and Diagnostic Hospital.

1. The term dysfunction is here used as synonymous with Sir Arthur Lovatt Evans' phrase, "a state of disease:" "A state of disease is never a thing in itself, but is always a quantitative change in some physiological process, an increase or diminution of something that was there to begin with." (Address of the President, Section 1, Physiology, British Association for the Advancement of Science, 1928.) Dysfunction, then, is a quantitative change whereby a function passes beyond physiologic limits, and arrest of dysfunction is a quantitative return of the process to within physiologic limits. Any less comprehensive term would be insufficient to include the wide range of phenomena observed. In many of these cases the arrest of a malady leaves no detectible trace of a pathologic process; it is as if no such process had existed; in others a residuum of the process remains, but soon disappears, as if the process had been arrested. In still other cases the pathologic process seems to be arrested for the time, but tends to recur at varying intervals. The most accurate term applicable to these varying phases would seem to be "dysfunction."

Anesthetization of the sphenopalatine ganglion is accomplished by topical application of 2 minims (0.12 cc.) of 50 per cent butyn to the lateral wall of the nasopharynx posterior to the tip of the middle turbinate.[2]

"A pinch of cotton is wound upon the tip of the applicator into a smooth, compact spindle about five millimeters in diameter at the center. This is dipped into the adrenalin and squeezed dry between the forefinger and thumb so as to flatten it in the same plane with the bent handle. At the same time the tip is bent to an angle of about thirty degrees in this plane. Two drops of butyn are added, and the applicator is now ready to be placed.

"Standing on the right side of the patient, with the left forearm resting upon the patient's head and the left forefinger slightly raising the tip of the nose, the operator introduces the applicator, coaxing it along the floor of the nose or wherever its passage is found to be easiest, to a depth of about two and three-quarter inches, when it will be felt to come into the open space of the nasopharynx. The curved tip is now rotated outward to an angle of about forty-five degrees, when it makes contact with the pharyngeal wall. It is left in this position for about five minutes, close watch being kept during this time to see that contact with the wall is continuous, when anesthesia of the sphenopalatine ganglion should be complete.

"Caution: During this process close observation should be made of an untried patient, and should any pallor, nausea, or other untoward symptom supervene, the test should be discontinued."

The act of anesthetization is unavoidably preceded by some nasal irritation incident to the introduction of an applicator into the nasopharynx. A number of phenomena, such as lacrimation, itching of the roof of the mouth, twitching of the alae of the nose, coughing, sneezing, the temporary augmentation of remote dysfunctions and sometimes relief from remote dysfunctions, are observed during this brief period of nasal irritation. Such phenomena, however, will not be considered here, as this article is limited to phenomena appearing when the ganglions become impervious to the passage of nerve currents, which occurs from two to five minutes after anesthetization.

The first recorded instance of a remote dysfunction arrested by anesthetization of the sphenopalatine ganglion occurred in a case of headache relieved by Sluder[3] in 1903. Subsequently such arrest of dysfunctions has been observed in the neck, trunk and extremities. It is in dysfunctions about the eyes, however, that these phenomena are

2. The authors' technic for anesthetization of the sphenopalatine ganglion (quoted from J. Michigan M. Soc. **29**:294 [April] 1930) is as follows: "Armamentarium: an applicator, absorbent cotton, adrenalin, and butyn. The applicator is of aluminum, and slender, with about two centimeters of the tip subjected to heat for pliability. The cotton should be of long fiber; the adrenalin, 1/1000; and the butyn a 50 per cent aqueous solution.

3. Sluder, Greenfield: Nasal Neurology, Headaches and Eye Disorders, St. Louis, C. V. Mosby Company, 1927.

most frequently noted. Sluder[3] said: "That the pain of all eye lesions may be stopped by cocain to the nasal ganglion . . . is a fact which has been repeatedly observed." This statement does not seem overdrawn. There are few, if any, pains in the eyes not represented in the list, and they are relievable in a majority of cases. Of the various pains and other dysfunctions of the eye and periocular structures that have been thus arrested we may mention more specifically: the pain of iritis, observed by Sluder,[3] Byrd[4] and Ryerson;[5] the pain of keratitis, observed by Sluder,[3] Byrd[4] and Ryerson;[5] the pain of interstitial keratitis associated with syphilis, observed by Byrd;[4] the pain of conjunctivitis, observed by Sluder,[3] Byrd[4] and Ryerson;[5] the pain of optic neuritis from methyl alcohol poisoning, observed by Byrd;[4] the pain of traumatic ulcer of the cornea, observed by Sluder[3] and Byrd;[6] blepharospasm, observed by Sluder;[3] functional hyperesthesia of the ciliary muscle, observed by Sluder;[3] pain in the eye associated with errors of refraction, observed by Byrd;[4] photophobia, observed by Sluder,[3] Byrd[4] and Ryerson;[5] excessive lacrimation, observed by Sluder,[3] Byrd[4] and Ryerson;[5] intra-ocular tension and pain of glaucoma, observed by Sluder,[3] Miller,[7] Byrd[8] and Ryerson;[5] the pain of phlyctenula, observed by Sluder[3] and Byrd,[4] and the pain of chalazion, observed by Byrd.[4] Dysfunctions of and about the ear include: the pain of otitis media, observed by Sluder[3] and Byrd;[4] chronic otorrhea, observed by Byrd;[4] otalgia, observed by Sluder,[3] Clerf,[9] Gugenheim,[10] Hansel,[11] Byrd[4] and Lillie;[12] mastoidalgia, observed by Sluder,[3] Lillie,[12] Cook[13] and Byrd;[4] itching of the external auditory canal, observed by Byrd[4] and Ruskin;[14] tinnitis aurium,

4. Unpublished cases of the authors.

5. Ryerson, F. L.: Personal communication to the authors.

6. Byrd, H.: Pathological Impulses or Currents, M. J. & Rec. **121**:141 (Feb.) 1925.

7. Miller, H. E., quoted by Sluder (footnote 3, p. 99).

8. Byrd, H.: Influence of Nasal Ganglion in Treatment of Glaucoma, Arch. Ophth. **56**:162 (March) 1927.

9. Clerf, L. H.: Control, Through the Nasal Ganglion, of Earache of Laryngeal Origin, J. A. M. A. **82**:630 (Feb. 23) 1924.

10. Gugenheim, L. K., quoted by Sluder (footnote 3, p. 273).

11. Hansel, F. K.: Otalgia from Abscess of the Tongue Controlled by Cocainization of the Nasal Ganglion, Arch. Otolaryng. **7**:165 (Feb.) 1928.

12. Lillie, H. W., quoted by Sluder (footnote 3, p. 273).

13. Cook, J. D.: Symptomatology of a Case of Sphenopalatine Ganglion Neurosis, J. Missouri M. A. **21**:319 (Sept.) 1924.

14. Ruskin, S. L.: The Nasal Ganglion in Relation to Itching of the Auditory Canal and Tinnitis Aurium, Arch. Otolaryng. **2**:269 (Sept.) 1925; Herpes Zoster Oticus Relieved by Sphenopalatine Ganglion Treatment, Laryngoscope **35**:301 (April) 1925.

observed by Byrd[4] and Ruskin;[15] progressive deafness, observed by Byrd;[4] sense of fulness of the ear, observed by Ruskin;[14] sense of fulness of the ear of allergic origin, observed by Byrd;[4] pain in the external auditory canal associated with fungus infection, observed by Byrd;[4] ear cough, observed by Byrd,[4] and herpes zoster oticus, observed by Ruskin.[16] Dysfunctions about the nose and throat that have been arrested include: the pain of maxillary, frontal and ethmoid sinusitis, observed by Sluder[3] and Byrd;[4] rhinorrhea, observed by Sluder[3] and Byrd;[4] acne rosacea, observed by Sluder[3] and Byrd;[4] toothache in the upper jaw, observed by Sluder[3] and Byrd;[4] parageusia, observed by Sluder[3] and Ruskin;[17] itching of the roof of the mouth, observed by Byrd;[4] unilateral burning sensation in the roof of the mouth, observed by Ruskin;[17] pain associated with Vincent's angina, observed by Byrd;[4] glossodynia, observed by Sluder,[3] Dean[18] and Engman;[19] the pain of follicular tonsillitis, observed by Byrd;[4] the pain of tonsillar diphtheria, observed by Byrd;[4] the pain of septic sore throat, observed by Byrd;[4] the pain of peritonsillar abscess, observed by Byrd[4] and Hoople;[20] postoperative pain, after tonsillectomy, observed by Byrd;[4] pain of tuberculous laryngitis, observed by Gundrum;[21] external cricoidynia, observed by Sluder,[3] and spasm of the esophagus, observed by Sluder.[3] As we pass from dysfunctions about the head to those of the trunk and extremities, we may mention: migraine, observed by Sluder[3] and Gundrum;[22] vertigo, observed by Byrd,[4] and nausea, observed by Byrd.[4] Among dysfunctions of the circulatory system that have been arrested to date are: angina pectoris, observed by Heitger[23] and Byrd;[4] hypertension, observed by Byrd,[4] Warren[24] and Ryerson;[5] Buerger's disease, observed by Chester;[25] tachycardia, observed by Goldschmidt-Osmund[26] and Byrd,[4] and cardiospasm, observed by Ruskin.[27]

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15. Ruskin (footnote 14, first reference).
16. Ruskin (footnote 14, second reference).
17. Ruskin, S. L.: Contributions to Study of the Sphenopalatine Ganglion, Laryngoscope **35**:87 (Feb.) 1925.
18. Dean, L. W.: The Control of Glossodynia, South. M. J. **15**:856 (Oct.) 1922.
19. Engman, M. F., quoted by Sluder (footnote 3, p. 273).
20. Hoople, G. D.: A New Method of Anesthesia for Opening Peritonsillar Abscess, Laryngoscope **36**:577 (Aug.) 1926.
21. Gundrum, L. K.: Pain from Tuberculous Laryngitis Relieved by Cocainization of the Nasal Ganglion, J. A. M. A. **83**:998 (Sept. 27) 1924.
22. Gundrum, L. K.: Migraine Controlled Through the Nasal Ganglion, Arch. Otolaryng. **8**:564 (Nov.) 1928.
23. Heitger, J. D., quoted by Sluder (footnote 3, p. 289).
24. Warren, E. W.: Personal communication to the authors.
25. Chester, John L.: Personal communication to the authors.
26. Goldschmidt-Osmund, Bruno, quoted by Sluder (footnote 3, p. 101).
27. Ruskin, S. L., quoted by Sluder (footnote 3, p. 279).

Respiratory dysfunctions arrested by anesthetizing the sphenopalatine ganglions include: hay-fever, observed by Sluder,[3] Payne,[28] Gundrum [29] and Byrd;[30] sneezing, observed by Byrd;[4] dyspnea, observed by Byrd;[4] hiccup, observed by Hansel,[31] Rehfeldt,[32] Costen [33] and Byrd;[4] cough, observed by Byrd,[4] and asthma, observed by Sluder,[3] Gundrum [34] and Byrd.[35] Passing to diseases of the lower trunk, we may note: chronic inguinal distress following herniotomy, observed by Byrd;[36] diarrhea, observed by Sluder;[3] renal colic, observed by Chester;[25] gallstone colic, observed by Chester;[25] frequent micturition, observed by Sluder;[3] pain of cystitis, observed by Sibley;[37] ovaritis, observed by Byrd[4] and Warren;[24] dysmenorrhea, observed by Byrd,[4] Warren [24] and Gundrum,[22] and the vomiting of pregnancy, observed by Warren.[24] Another group of dysfunctions arrested includes: chronic sore spots at the lower border of the ribs, the coccyx, the cervical lymphatics, the breast and the larynx, observed by Byrd,[38] and the pain of cancer of the uterus, breast and larynx and just below the left clavicle, observed by Byrd.[38] Rheumatoid dysfunctions arrested by anesthetizing the sphenopalatine ganglion include: sciatica, observed by Byrd [39] and Ruskin;[17] neuritis, observed by Byrd;[4] pleurisy, observed by Byrd;[4] lumbago, observed by Sluder,[3] Byrd [40] and Saunders;[41] the pain of arthritis, observed by Byrd;[42] the pain of gout, observed by Byrd;[4] the pain of bunions,

28. Payne, R. J.: Treatment of Nasal Ganglion in Hay Fever, J. Missouri M. A. **21**:257 (Aug.) 1924.

29. Gundrum, L. K.: Nasal Ganglion Neuroses, California & West. Med. **24**:204 (Feb.) 1926.

30. Byrd, H.: Hay Fever, Its Control Through Efferent Interception, Ann. Int. Med. **3**:850 (Feb.) 1930; Hay Fever, Its Surgical Conquest, Laryngoscope, to be published.

31. Hansel, F. K., quoted by Sluder (footnote 3, p. 275).

32. Rehfeldt, C. S.: Control of Intractable Singultus (Hiccough) Through the Nasal Ganglion, Laryngoscope **35**:354 (May) 1925.

33. Costen, J. B.: Persistent Hiccough: Control by Cocainization of the Nasal Ganglion, Ann. Otol. Rhin. & Laryng. **37**:860 (Sept.) 1928.

34. Gundrum, L. K.: Asthma and Eczema Controlled Through the Nasal Ganglion, Ann. Clin. Med. **4**:573 (Jan.) 1926.

35. Byrd, Hiram; and Byrd, Wallace: The Clinic as a Field for Biologic Research, Clin. Med. & Surg. **37**:95 (Feb.) 1930. Byrd, H.: The Sphenopalatine Test, J. Michigan M. Soc. **29**:294 (April) 1930.

36. Byrd (footnote 35, second reference).

37. Sibley, C. P.: Personal communication to the authors.

38. Byrd, H.: Pathological Currents and Cancer, J. Cancer Research **3**:13 (Oct.-Dec.) 1926; footnote 4.

39. Byrd (footnotes 4 and 35).

40. Byrd, H.: Blocking Off Remote Pain at the Nasal Ganglia, M. J. & Rec. **120**:126 (suppl.) (Oct. 15) 1924; footnote 36.

41. Saunders, D. U.: Personal communication to the authors.

42. Byrd (footnote 4; footnote 40, first reference).

observed by Byrd,[4] and, perhaps of a similar nature, pain associated with flatfoot, observed by Byrd.[4] The motor dysfunctions arrested include: writer's cramp, observed by Sluder;[3] professional cramp, observed by Sluder;[3] motor weakness of the forearm, observed by Sluder,[3] and chorea of the arm and the leg, observed by Byrd.[43] Other dysfunctions arrested by anesthetizing the sphenopalatine ganglion are: the pain and soreness of a surgical and infected hand, observed by Byrd;[6] pruritus vulvae, observed by Byrd,[4] and eczema, observed by Gundrum.[34] In addition, a great variety of less sharply defined dysfunctions have been arrested. These include neuralgic and rheumatoid pains throughout the head, neck, trunk and extremities, observed by Sluder,[3] Byrd[42] and others. A conception of the wide range of dysfunctions arrested by anesthetizing the sphenopalatine ganglion is given

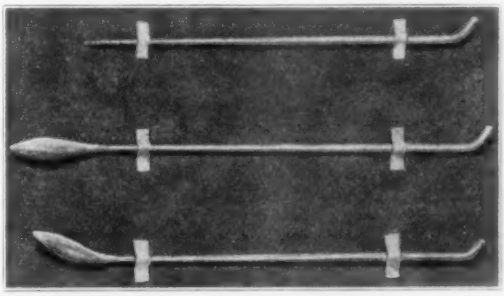

Fig. 1.—The upper figure is an aluminum applicator with a curved handle and a softened tip. The center figure shows a pledget of cotton wound on the applicator in spindle form, and the lower figure shows the pledget of cotton properly flattened and curved for introduction.

in Dock's masterly paper read before the American Medical Association in July, 1929.[44]

It may be noted that the dysfunctions arrested involve the following categories: sensory, motor, secretory, respiratory and circulatory. In the light of this one would expect the endocrine dysfunctions to be similarly arrested. The following case, seen with Dr. H. J. Jensen, of Tampa, Fla., is offered for whatever significance the reader wishes to attach to it.

Mrs. T., when first seen, was suffering from pain in the head and eyes, with a general tremor. The pulse rate was 180 per minute. She complained of having had disagreeable symptoms for four years, with periods of excessive

43. Byrd, H.: Chorea, Arch. Otolaryng. **7**:257 (March) 1928.

44. Dock, George: Sluder's Nasal Ganglion Syndrome and Its Relation to Internal Medicine, J. A. M. A. **93**:750 (Sept. 7) 1929.

hunger, sometimes associated with periods of blurred vision, which she called "blind spells." She had been much worse for the past three weeks, and had been without sleep for the past forty-eight hours. At this time she had severe pain about the left cheek and eye, and both swelling and tenderness in the thyroid region. The left sphenopalatine ganglion was anesthetized. Within five minutes the patient was free from pain, relaxed and sleepy. When seen after four hours of sleep, she was still comfortable. The swelling and tenderness of the thyroid area had somewhat abated. She slept soundly that night, and when seen the next morning was only moderately hungry, free from pain and feeling generally well. She was kept in bed on a light diet for ten days without treatment. During this interval, the cervical swelling and tenderness gradually reappeared, together with the former symptoms—pain, tremor, hunger and tachycardia. With the patient under general anesthesia, 95 per cent alcohol was injected into the left sphenopalatine ganglion. On the following day, the patient resumed her normal activities, free from all symptoms. At the end of nine months there had been no recurrence.

Before entering into a discussion of these phenomena, it seems pertinent to indicate what is meant by a dysfunction being relieved. We do not consider a dysfunction relieved unless the relief is complete and occurs within five minutes from the placement of the anesthetic. Cases in which the patient experiences merely improvement, even though quite distinct, are considered negative, because in our experience such cases tend to show less and less reaction to subsequent treatments.

In this connection it should be noted that the relief is generically different from that obtained by the administration of drugs. This difference appears in the rapidity with which relief is obtained, in its completeness and particularly in the fact that it is not accompanied by any unnatural sensations, nor followed by any physiologic after-effects that we can detect, but leaves the patient feeling as if the dysfunction had never existed.

For mechanical reasons, however, certain types of patients, although relieved from active symptoms, continue to present a residuum of dysfunction until physiologic repairs can be effected. For instance, when postoperative pain is relieved by anesthetization of the sphenopalatine ganglion, the wound is still sensitive to pressure. In arthritis, when hyperplasia has occurred some remaining soreness in the joint is to be expected; in asthma, though the dyspnea is immediately relieved, the excess secretions in the lungs cause a residuum of irritation that may last for several hours.

The presence of a residuum of sensitiveness raises a most significant question: Is this relief brought about by cutting the sensory path from the affected locus to the brain, i. e., by intercepting the message of pain, or must it be ascribed to some other cause? Consideration of this question, however, will be deferred until the end of the article.

REGIONS

On the basis of sphenopalatine phenomena, three anatomic regions are observed: two lateral halves above the neck and the rest of the body. Above the neck dysfunctions are arrestible with somewhat greater frequency than below, and always from the same side. In general, it may be said that dysfunctions below the neck are arrestible from the ganglion of the same side, the opposite side or neither. Certain specific dysfunctions, however, appear to be more frequently arrested from one side than from the other. Sciatica and the rheumatoid dysfunctions, for example, tend to be arrestible, if at all, by anesthetization of the left sphenopalatine ganglion, while asthma is seldom if ever arrested except from the right. Angina pectoris, as far as we know, has been arrested only from the left.

DURATION

In a case of chorea [43] it was found that anesthetization of the sphenopalatine ganglion uniformly kept the malady in abeyance for a period of four hours. From this and similar experiences it is inferred that four hours is the life of the anesthetic when used in this connection.

The four hour interval has given us an important dividing line: Patients in whom the relief lasts four hours or more tend to recover under repeated anesthetization, while those in whom the relief lasts less than four hours tend to become less and less amenable to this type of treatment.

DIVERSITY OF EFFECTS

From what has been said it is apparent that in the presence of almost any dysfunction, near or remote, the sphenopalatine ganglion may be anesthetized with some hope of relief. In some cases it succeeds, and in others it fails; however, it should be noted that in a few cases it more than fails, actually augmenting or even initiating a dysfunction.

Sluder [3] was the first to observe the augmentation of a dysfunction by anesthetization of the sphenopalatine ganglion, as shown in deep temporal headache. Our experience has confirmed this observation in a number of cases, but has not extended it to other dysfunctions. Sluder cited Pollock [45] as having initiated sciatica by injection of the sphenopalatine ganglions. Our experience does not include the initiation of any rheumatoid dysfunctions, either by injection or by anesthetization. We have observed fainting, nausea, palpitation, dyspnea,[4] and an urticaria-like eruption as rare manifestations that could not be explained as drug hypersensitiveness, since they were not precipitated by similar application on the opposite side. Dr. George Dock [46] has observed an uncontrollable impulse to press the teeth together without

45. Pollock, H. L., quoted by Sluder (footnote 3, p. 276).

46. Dock, George: Personal communication to the authors.

grinding brought on temporarily by anesthetization of the sphenopalatine ganglion. It is reassuring, however, to note that the percentage of cases in which dysfunctions are augmented or initiated is small. In a series of more than 10,000 anesthetizations [4] less than 20 such instances have been observed.

PROPORTIONS

From the considerable list of dysfunctions arrested by anesthetizing the sphenopalatine ganglion it is not to be inferred that the symptoms are thus arrestible in every case, but merely that an arrestible one occurs here and there. Of two indistinguishable cases of sciatica, for example, it will be found that one can be arrested by anesthetizing the sphenopalatine ganglion, while the other cannot. The same is true of angina pectoris, chorea, asthma, and so on, throughout the whole category.

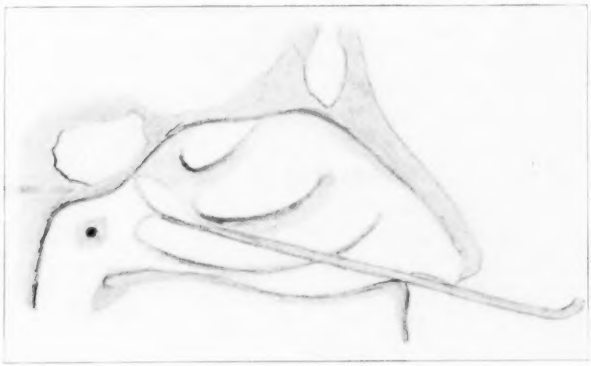

Fig. 2.—Side view of the lateral wall of the nasal chamber, with applicator in place.

In painful afflictions of the eye a considerable majority of cases may be expected to be relieved, and in dysfunctions about the maxillary sinus, the frontal sinus and the tonsillar fossae perhaps a majority may be relieved. In dysfunctions of the ear, such as otitis media, earache and progressive deafness, the proportion is somewhat less, while for the most part, dysfunctions below the neck show a still smaller proportion of positive reactions. A notable exception is lumbago, which appears to be relieved in an ample majority of cases. Dr. Saunders,[41] at Eloise Infirmary where anesthetization of the sphenopalatine ganglion for lumbago is now a routine procedure, is of the opinion that relief may be expected in fully three fourths of the cases. In sciatica, however, our experience indicates that the proportion is about 1:4 or 1:5. In hypertension the percentage seems to be a little higher and in asthma a little lower.

THERAPEUTIC APPLICATION

When a sphenopalatine ganglion is anesthetized and a dysfunction arrested, the first question that presents itself is whether the relief will be permanent. In some cases it will. In a large majority of cases of lumbago, for example, whenever the sphenopalatine reaction is positive, the lumbago never returns. In noninfectious iritis ("cold settled in the eye") anesthetization of the ganglion of the same side relieves all the discomfort, while a drop of epinephrine relieves the congestion so that in a period of five minutes the eye is brought to what seems to be a normal state. In a great majority of such cases there is no recurrence of the symptoms.

All cases are not so readily amenable, however. Sciatica, for example, may be relieved and later return, requiring two, three, four or more anesthetizations before there is final cessation of the disturbance. In some instances a dysfunction may continue to return even after repeated anesthetizations, each of which arrests it for four hours or more. For these, the injection of alcohol into the strategic ganglion is indicated. Thus the patient with chorea, whose case was cited, was always relieved for four hours by anesthetization of the left sphenopalatine ganglion, and was finally given permanent relief by the injection of alcohol.

It should also be noted that in some cases relief for four hours or more is obtained for a time, but after a number of days or weeks some change occurs, whereupon the ganglion suddenly ceases to be strategic, and no relief can be obtained by its anesthetization. This phenomenon is especially frequent in cases of asthma. For example, in the case [4] of Mrs. G., who had had asthma for the past year, the right sphenopalatine ganglion was anesthetized during a desperate attack. The relief was complete within five minutes and lasted twelve hours. Subsequent attacks during the ensuing two weeks were similarly arrested, the respite lasting uniformly for four hours or more. The question in mind was whether it was not time to inject alcohol into the ganglion. This question was soon answered in the negative, however, by an attack in which anesthetizing the ganglion failed to give any degree of relief. Henceforth any therapeutic approach to the case via the sphenopalatine ganglion was futile.

In contrast with this, Mrs. R. had been a sufferer from asthma for more than forty years when it was found that anesthetizing the right sphenopalatine ganglion during an attack arrested it. Four or five other anesthetizations whenever the asthma recurred during the next few months effected relief which has lasted for five years.

Similarly, in a recent case of sciatica (H3260), the patient was relieved in midattack by anesthetization of the left sphenopalatine gan-

glion; after three such anesthetizations, he has been free from the malady for four months. On the other hand, in the next case that appeared, outwardly indistinguishable from the first, the patient did not obtain the slightest relief.

FUTILITY OF FREQUENT REINJECTION

References in the literature to reinjection of the sphenopalatine ganglions with alcohol at brief intervals call for some comment. It seems to be a generally accepted fact that the injection of alcohol into a nerve defunctionizes it for a number of months, roughly a year. We have no reason for supposing that the sphenopalatine ganglion is any exception to this general rule. Hence, to make reinjections before the effect of the previous injection is gone would be like reanesthetizing while anesthetization is still in effect. Our experience seems to confirm this.

THE SPHENOPALATINE TEST

Since the effect of anesthetization and injection may be considered the same except in duration, anesthetization affords a ready test to determine whether the injection of alcohol is indicated. Injections should never be made into the ganglion except on the basis of the sphenopalatine test;[36] that is, injection should be made only when it has been shown on a number of occasions that anesthetization relieves the dysfunction immediately (from two to five minutes), completely and for a period of four hours or more.

The sphenopalatine test is applicable in the determination of the advisability, not only of injections, but of proposed reinjections. A positive sphenopalatine test within a few days or weeks after an injection has been made into the ganglion shows that the injection missed its mark, while a positive test ten months or a year after an injection shows that the effect of the injection has passed away. In either case reinjection is permissible.

One should never be in haste to make injections, but should apply the sphenopalatine test from six to a dozen times beforehand. In most cases, after a series of anesthetizations it will be found that the dysfunction has either been relieved indefinitely or has ceased to be amenable to this type of procedure. Few injections are really indicated.

THE PATH OF PAIN NOT OBSTRUCTED

It is demonstrable that when pain is relieved by anesthetization of the sphenopalatine ganglion the locus of distress is not anesthetized. The cornea that is relieved from the pain of a corneal ulcer is still just as sensitive to a wisp of cotton as the cornea of the opposite eye. The pain associated with an inflamed and bulging ear-drum may be relieved,

but paracentesis immediately afterward is none the less painful.[47] The pain of sciatica, arthritis, gout, bunions or even of an acute infection [48] may be relieved, but sensitiveness in the region of distress is not detectibly blunted.

Hoople [20] mentioned having anesthetized the sphenopalatine ganglion in the presence of a peritonsillar abscess, thus producing anesthesia of the tonsillar area so that the abscess could be opened. Although we entertain the greatest respect for this observer, our own observations lead us to doubt whether a critical examination would reveal any anesthesia in the tonsillar region incident to anesthetizing the sphenopalatine ganglion. This doubt is based on several considerations:

1. We have many times anesthetized the ganglion in the presence of a normal tonsil and have endeavored without success to demonstrate even a slight trace of anesthesia in the tonsillar area.[49]

Fig. 3.—Profile, showing applicator in place.

2. We have repeatedly opened peritonsillar abscesses with relatively little pain after anesthetization of the sphenopalatine ganglion, whereas before anesthetization such a procedure would have been impossible. Yet in such cases we have been unable to demonstrate any anesthesia in the affected tonsil as compared with the tonsil of the opposite side. What did happen was that the pain and soreness incident to the abscess were relieved by anesthetization of the sphenopalatine ganglion of the same side, the area being thus converted from one of great distress to one of relative comfort. Under these circumstances the pain when a peritonsillar abscess is opened apparently is not intolerable.

3. If it were true that anesthetizing the sphenopalatine ganglion gave relief through producing anesthesia of the affected region, all

47. Sluder (footnote 3). Byrd (footnote 4).

48. Byrd (footnote 4). Pollock (footnote 45).

49. Whenever the ganglion has been anesthetized for any purpose, the following simple test for tonsillar anesthesia is suggested: With an applicator carrying a wisp of cotton compare the two tonsils for sensitiveness.

regions in which dysfunctions may be potentially relieved would pass into a state of anesthesia whenever the ganglion was anesthetized; since these regions include all the major ones of the body, such anesthesia would be widespread. Moreover, if this were true, the injection of alcohol into the ganglion would make this widespread anesthesia persist for a number of months. Such effects are not in accordance with clinical experience.

Whatever may be the mechanism by which pain is relieved when the sphenopalatine ganglion is anesthetized, it is not anesthesia of the erstwhile locus of distress, i. e., not obstruction of the sensory path.

CONCLUSION

Dysfunctions numbering more than threescore have been relieved by anesthetization of the sphenopalatine ganglions, including afflictions as intractable as progressive deafness, as painful as migraine and iritis and as grave as glaucoma and angina pectoris. A therapeutic measure which results in the mastery of a serious disease, such as diphtheria or diabetes, is hailed as a victory. Anesthetization of the sphenopalatine ganglion does not give relief in all cases of any one malady, but may be confidently expected to do so in at least one fifth of all cases of the several serious afflictions mentioned, which is equal to relief in all cases of one of them. Besides this, anesthetization of the sphenopalatine ganglion gives relief in a certain percentage of cases of more than threescore other dysfunctions, ranging from sciatica and pruritus to chorea and hypertension.

Furthermore, while anesthetization of the sphenopalatine ganglion has not in itself accomplished the conquest of any one disease, it has led directly to the therapeutic mastery of hay-fever, vasomotor rhinitis and polypoid degeneration.

A procedure which gives relief in even a moderate proportion of cases of more than threescore dysfunctions and in a majority of cases of certain others must have a sum total of therapeutic usefulness of the first magnitude, especially as it displaces no existing device in our armamentarium.

We believe that anesthetization of the sphenopalatine ganglion should be a routine procedure in every one of the dysfunctions enumerated, not only as a preliminary test, but as a therapeutic measure in cases that show a positive reaction. The sum total of its usefulness is such that it should command the attention of every one who engages in the practice of medicine.

2201 Jefferson Avenue East.

SERUM TREATMENT FOR CHRONIC ULCERATIVE COLITIS *

J. ARNOLD BARGEN, M.D.

EDWARD C. ROSENOW, M.D.

AND

GEORGE F. C. FASTING, M.D.

ROCHESTER, MINN.

One of the most severe, debilitating infections is chronic ulcerative colitis of the type in which we [1] have shown a diplostreptococcus to have etiologic significance. Its onset may be insidious, beginning with the passage of blood, mucus and pus, mixed with the stool, at times associated with abdominal cramps and tenesmus, but not necessarily with marked increase in the number of passages. It may also start as a severe, fulminating illness, with many bloody, rectal discharges mixed with pus, with gruelling cramps, fever (figs. 1 and 2), and marked prostration, somewhat in the manner of other severe infectious diseases.

CORRECTION

In this issue the headings at the tops of some of the pages of the article by Bargen et al. and of that by Wolferth and Margolies have been accidentally transposed.

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1930.

* From the Division of Medicine and the Division of Experimental Bacteriology, the Mayo Foundation.

1. Bargen, J. A.: Changing Conceptions of Chronic Ulcerative Colitis, J. A. M. A. **91**:1176 (Oct. 20) 1928; Chronic Ulcerative Colitis: A Review of Investigation on Etiology, Arch. Int. Med. **45**:559 (April) 1930.

2. Buie, L. A.: Chronic Ulcerative Colitis, J. A. M. A. **47**:1271 (Oct. 16) 1926. Carman, R. D., and Moore, A. B.: The Roentgenologic Findings in Ulcerative Colitis, Am. J. Roentgenol. **16**:17 (July) 1926.

3. Bargen, J. A., and Weber, H. M.: Regional Migratory Chronic Ulcerative Colitis, Surg. Gynec. Obst. **50**:964 (June) 1930.

4. Bargen, J. A.: Specific Serum Treatment in Chronic Ulcerative Colitis, Arch. Int. Med. **43**:50 (Jan.) 1929.

regions in which dysfunctions may be potentially relieved would pass into a state of anesthesia whenever the ganglion was anesthetized; since these regions include all the major ones of the body, such anesthesia would be widespread. Moreover, if this were true, the injection of alcohol into the ganglion would make this widespread anesthesia persist for a number of months. Such effects are not in accordance with clinical experience.

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ROCHESTER, MINN.

One of the most severe, debilitating infections is chronic ulcerative colitis of the type in which we [1] have shown a diplostreptococcus to have etiologic significance. Its onset may be insidious, beginning with the passage of blood, mucus and pus, mixed with the stool, at times associated with abdominal cramps and tenesmus, but not necessarily with marked increase in the number of passages. It may also start as a severe, fulminating illness, with many bloody, rectal discharges mixed with pus, with gruelling cramps, fever (figs. 1 and *2*), and marked prostration, somewhat in the manner of other severe infectious diseases. Between the two extremes are all gradations of seriousness in symptoms, which depend, in large measure, on the extent of involvement of the large intestine. The disease affects various portions, or all, of the large intestine but, except later in the severer cases, rarely attacks the terminal portion of the ileum.[2] Clinical, proctoscopic and roentgenologic evidence supports the assumption that the disease usually starts in the rectum. However, any portion of the large intestine may be affected.[3]

We have reported previously on the use of specific vaccines and serum as part of the treatment for this disease.[4] The type of case most suitable for treatment by specific vaccines has been described. We have

* Submitted for publication, April 15, 1930.

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1930.

* From the Division of Medicine and the Division of Experimental Bacteriology, the Mayo Foundation.

1. Bargen, J. A.: Changing Conceptions of Chronic Ulcerative Colitis, J. A. M. A. **91**:1176 (Oct. 20) 1928; Chronic Ulcerative Colitis: A Review of Investigation on Etiology, Arch. Int. Med. **45**:559 (April) 1930.

2. Buie, L. A.: Chronic Ulcerative Colitis, J. A. M. A. **47**:1271 (Oct. 16) 1926. Carman, R. D., and Moore, A. B.: The Roentgenologic Findings in Ulcerative Colitis, Am. J. Roentgenol. **16**:17 (July) 1926.

3. Bargen, J. A., and Weber, H. M.: Regional Migratory Chronic Ulcerative Colitis, Surg. Gynec. Obst. **50**:564 (June) 1930.

4. Bargen, J. A.: Specific Serum Treatment in Chronic Ulcerative Colitis, Arch. Int. Med. **43**:50 (Jan.) 1929.

found the use of whole immune horse serum unsatisfactory because of the frequent severe "serum sickness" which results from its administration in doses sufficient to produce results. That the course of the disease has been favorably influenced in many of the very sick patients,

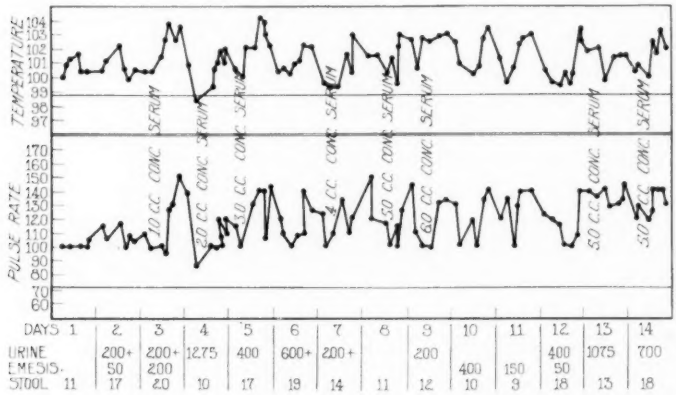

Fig. 1.—Data concerning the condition of the patient represented by case 29 (tabulation) during her first two weeks in the hospital.

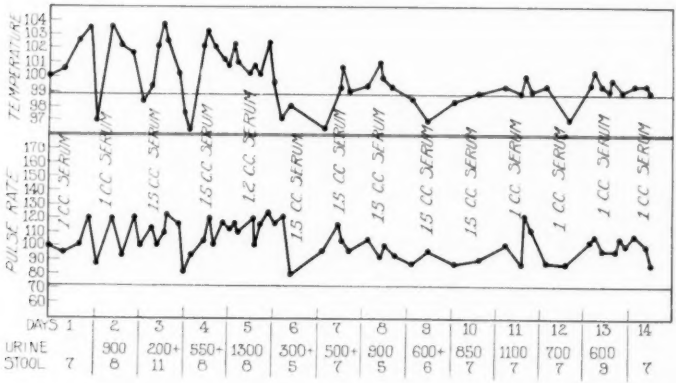

Fig. 2.—Data concerning the condition of the patient represented by case 9 (tabulation), during her first two weeks in the hospital. The fever subsided when treatment was begun.

has been shown in a sufficiently large number of cases to make it urgent that the factor which causes the distressing "serum sickness" be reduced, or, if possible, entirely removed.

The serum has been prepared by injecting into horses, increasing doses of freshly isolated strains of the diplostreptococcus, and by using many of these strains after they have been preserved, during the period of immunization, in dense suspensions in a mixture of two parts of glycerin and one part of a solution of sodium chloride, 25 per cent. This method has been shown to preserve specificity of the streptococci for a long time. Intravenous injections were given on three successive days each week, beginning with 5,000,000,000 dead organisms. The dosage was gradually increased to 2,000,000,000,000 organisms. After immunization had been continued for from two to four months, live organisms were given. Bleedings were made from seven to ten days after the last previous injection, at intervals of from three to six weeks, depending on the condition of the animal. The bleedings were made in a sterile manner from the jugular vein. The serum was drawn from the clotted blood after the clot had been squeezed with tinned weights for from twenty-four to forty-eight hours, and had been proved sterile by making aerobic, partial-tension and anaerobic cultures, as well as by inoculation of animals. The serum was used after immunization had been continued for months and not until it had a high agglutinating and precipitating titer, as well as protective power against the experimental disease in rabbits.

Because the administration of this serum caused a decidedly favorable influence on the course of severe, fulminating cases of chronic ulcerative colitis, it seemed highly important that some simple method be devised of preparing its effective portion so that its administration could be continued over a considerable period. Felton [5] has prepared a satisfactory product for use in pneumonia by a simple method of concentration of antipneumococcus serum. Following his suggestions, one of us (G. F. C. F.[6]) has prepared an antibody solution from whole serum of chronic ulcerative colitis by methods similar, in some ways, to Felton's, but more satisfactory in many essentials for our purpose.

One part of immune serum is diluted with ten parts of acidulated 5 per cent ether-water. The reaction is kept at a hydrogen ion concentration near 7. At a hydrogen ion concentration of 7, immune chronic ulcerative colitis serum yields a modified euglobulin containing essential antibodies. This euglobulin settles out in a few hours, is collected, and is dissolved in a mixture of glycerin and salt. The concentration of glycerin and salt is sufficiently high to act as a preservative. The con-

5. Felton, L. D.: A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera, Boston M. & S. J. **90**:819 (May 15) 1924.

6. Fasting, G. F. C.: On the Concentration of Antistreptococcus Serum, J. Infect. Dis. **45**:360 (Nov.) 1929.

centrated material is diluted with water and brought to a hydrogen ion concentration of 7.8. The refined serum used for injection into patients is made to contain about 2 mg. of nitrogen in each cubic centimeter.

The strikingly successful results that this material has yielded and the absence of the former distressing systemic serum-effect have led us to extend its use from the severe cases of acute illness to the more chronic and more resistant cases. In the strictest sense there is no such condition as "acute" ulcerative colitis of this bacterial type. The distinction is merely a matter of degree of chronicity. This fact must be kept in mind in the treatment in these cases.

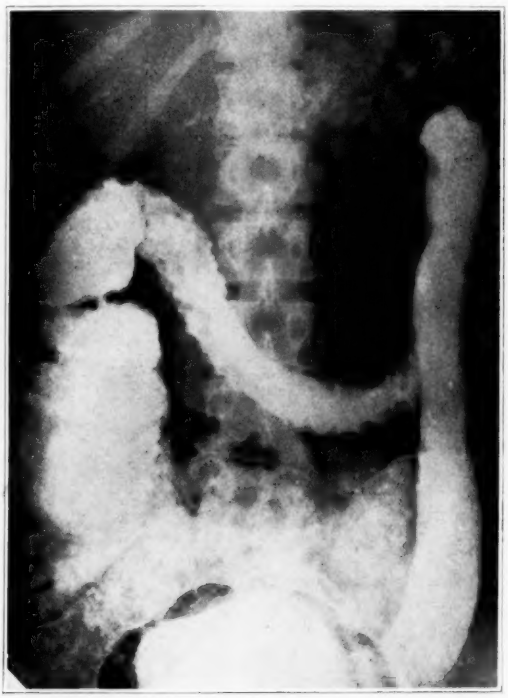

Fig. 3.—Roentgenogram after the administration of a barium enema, obtained in case 9 (tabulation). Extensive deformity and irregular mucosal edges corresponding to the deeper ulcerations are evident.

The antibody euglobulin solution has now been administered in approximately 200 cases of chronic ulcerative colitis. It is given deeply in the muscles. We feel that the earlier cases have been under observation sufficiently long to justify an expression of opinion as to the value

of this form of treatment, and with this idea in mind we are reporting the first 50 consecutive cases in which this concentrated serum or antibody solution was employed.

The accompanying table illustrates the salient features of all the cases.

COMMENT

The ages of the fifty patients ranged between 16 and 60 years, but twenty-seven of them were under the age of 30. The duration of the disease varied from six months to eighteen years, but in only nine cases had symptoms been present for less than a year. In thirty-three of the

A B

Fig. 4.—Roentgenograms after the administration of a barium enema obtained in case 5 (tabulation): *A*, the defects and irregularities present on first admission; *B*, the appearance after treatment.

fifty cases, the entire large intestine or the large intestine and the terminal portion of the ileum were involved by the infection. In five, the large intestine from the anus to the hepatic flexure was involved; in two, from the anus to the splenic flexure; in five, from the anus to the middle of the descending colon, and in only five was there no evidence of the disease in roentgenograms made after a barium enema (figs. 3 and 4 and table). The degree of anemia in most of the cases suggests the severity of the disease.

In seventeen cases, there were complications, including multiple polyps, rectal stricture, perirectal abscess, severe intestinal hemorrhage, arthritis, erythema nodosum, endocarditis and duodenal ulcer. It is

Summary of Serum Treatment in Fifty Cases

Case	Age and Sex	Duration of Disease, Years	Extent of Disease, Roentgenologically	Grade by Proctoscope	Hemoglobin, per Cent	Culture		Primary Improvement, per Cent	Comment
						Rectal Mucosa	Blood		
1	36F	2	From anus to middle of descending colon	2	43	+	..	100	Recurrence; treated with vaccine; quick recovery; free from symptoms at last report
2	42F	1.33	From anus to hepatic flexure	3	38	+	..	100	Had remained free from symptoms at last report
3	25F	5	Entire colon and terminal ileum	3	64	+	..	100	Complicated by erythema nodosum; had remained free from symptoms at last report
4	34F	2	Entire colon and terminal ileum	3	43	+	..	75	Complicated by polyps; originally 20 bloody stools each day; at last report 5 without blood
5	28M	6	From anus to hepatic flexure	2	49	+	..	100	Recurrence after one year; prompt control by vaccine; free from symptoms at last report
6	60M	0.5		2	78	+	..	100	Had remained free from symptoms at last report
7	17M	3	Entire colon and terminal ileum	3	58	+	..	Slight	Originally severe hemorrhages; at last report bleeding stopped, but little change in number of stools
8	63M	0.5		3	80	+	..	100	Had remained free from symptoms at last report
9	22F	3	Entire colon	3	..	+	..	100	Complicated by perirectal abscess; recurrence in nine months; treated again by antibody solution; almost free from symptoms at last report
10	22F	2	Entire colon	2	40	+	..	100	Had remained free from symptoms at last report
11	25F	2	Entire colon	2	40	+	..	100	Complicated by endocarditis; recurrence; controlled by vaccine; free from symptoms at last report
12	29F	1	From anus to middle of descending colon	2	70	+	..	100	Had remained free from symptoms at last report
13	34F	1		1	70	+	..	100	Had remained free from symptoms at last report
14	18F	3	Entire colon and terminal ileum	2	54	+	..	100	Had remained free from symptoms at last report
15	42F	6	Entire colon	2	68	+	..	100	Had remained free from symptoms at last report
16	16F	3	Entire colon	2	57	+	..	100	Had remained free from symptoms at last report
17	18M	2	Entire colon	2	61	+	..	100	Had remained free from symptoms at last report
18	57M	0.25	Entire colon	2	30	+	..	100	Had remained free from symptoms at last report
19	31M	3.5	Entire colon	2	65	+	..	75	Recurrence; on last report condition improved
20	40M	3	Entire colon	2	45	+	..	100	Had remained free from symptoms at last report
21	30M	2	Entire colon	2	42	+	..	75	Carrying on usual occupation at last report
22	29M	0.66	From anus to hepatic flexure	3	45	+	..	100	Recurrence; controlled by vaccine; free from symptoms at last report
23	42F	5	From anus to middle of descending colon	2	65	+	..	50	Improved at last report
24	42F	1	Entire colon and terminal ileum	2	30	+	..	None	Refused ileostomy; condition unchanged at last report
25	22F	1.5	Entire colon and terminal ileum	2	65	+	..	75	Recurrence; taking vaccine at intervals and condition improved at last report
26	54F	2	Entire colon	2	56	+	..	50	Colostomy performed because of complicating rectal stricture; improved
27	21F	1	Entire colon	2	38	+	..	50	Complicated by adenomatous goiter with hyperthyroidism; improved at last report

28	26F	3	Entire colon	2	40	+	..	None	Refused ileostomy; condition unchanged at last report
29	26F	1	Entire colon and terminal ileum	2	55	+	..	100	Complicated by perirectal fistula; recurrence; controlled by vaccine; free from symptoms at last report
30	28F	13	Entire colon	2	68	+	..	75	Complicated by polyps; marked improvement on last report
31	27M	0.5	From anus to hepatic flexure	2	60	+	..	75	Free from symptoms at last report
32	22M	5	Entire colon	3	55	+	..	75	Complicated by arthritis; originally 20 bloody stools each day; last report 4 without blood
33	24M	2	Entire colon	3	52	+	..	90	Recurrence; ileostomy elsewhere
34	40M	11	Entire colon	3	70	+	..	75	Improved at last report
35	36M	0.75	Entire colon	2	37	+	..	75	Complicated by exsanguinating hemorrhage; recurrence; ileostomy elsewhere
36	60M	0.75	.....	2	66	+	..	100	Complicated by duodenal ulcer; recurrence; improved by vaccine; free from symptoms at last report
37	34M	10	From anus to splenic flexure	2	60	+	..	75	Subsequently markedly improved; relapse with influenza; improved at last report
38	23M	0.75	Entire colon and terminal ileum	2	23	+	..	Slight	Complicated by repeated hemorrhages; refused ileostomy; at last report condition little changed
39	32M	1.5	Entire colon and terminal ileum	3	60	+	..	50	Ileostomy because of complicating polyposis and extreme rectal stricture; improved at last report
40	24F	2	Entire colon and terminal ileum	3	42	+	..	50	Complicated by polyposis and moderate rectal stricture; operation inadvisable; at last report number of stools reduced by one half and bleeding stopped
41	33M	6	Entire colon	3	40	+	..	Slight	Complicated by polyposis and rectal stricture; ileostomy before coming to clinic; at last report condition same as at dismissal
42	29M	3	From anus to splenic flexure	3	59	+	..	100	Complicated perirectal abscess; free from symptoms at last report
43	23F	1	Entire colon	3	43	..	..	None	Complicated by stricture and polyposis; condition unchanged at last report
44	32M	8	From anus to hepatic flexure	2	78	+	..	75	Complicated by polyposis; originally from 10 to 12 bloody stools each day; at last report reduced to from 2 to 4 without blood
45	20M	3	Entire colon	2	80	+	..	100	Cecostomy before coming to clinic; cecostomy closed surgically after treatment; free from symptoms at last report
46	53M	0.75	From anus to middle of descending colon	2	70	+	..	100	Had remained free from symptoms at last report
47	28F	2	.....	1	58	+	..	75	Free from symptoms at last report
48	49F	8	From anus to middle of descending colon	2	80	+	..	90	At last report from 2 to 3 stools each day instead of usual 1 before illness; otherwise free from symptoms
49	35F	18	Entire colon	2	78	+	..	100	Had remained free from symptoms at last report
50	21F	3	Entire colon	4	40	+	..	100	Ileostomy before serum used; at last report, 75 per cent improved

impossible to evaluate the effect which these conditions had on the progress of the disease or its treatment without the privilege of personal observation of the patients, but suffice it to say that in some instances they had a profoundly unfavorable effect on the result of the treatment. These are not selected cases, but rather fifty consecutive cases in which the antibody solution was given. However, only four of the twenty-four patients who became free from symptoms had complications, and these complications were of the less severe type. The suggestion is ventured that patients with uncomplicated cases of chronic ulcerative colitis are best treated by attempts to immunize against the causative organism. Results with this form of treatment far surpass other methods, including operation and irrigation of the colon with medicated solutions.

All the patients are living more than a year after treatment with the antibody solution except the one who died following operation for a ruptured appendix several months after becoming free from symptoms of chronic ulcerative colitis.

Twenty-four patients became free from symptoms; thirteen became from 75 per cent to 90 per cent well, and six were improved at least 50 per cent. In only seven cases was there little if any change following the treatment. These seven cases were either severe, long-standing cases with extensive involvement of the colon and destruction, or there were serious complications, such as multiple polyps or strictures.

Certain factors seemed to have a bearing on recurrence of symptoms after patients had become clinically well. One of the significant features seemed to be the failure to remove possible foci of infection. Acute infections of the upper part of the respiratory tract are poorly borne by patients who once have had chronic ulcerative colitis. The extent of involvement, the length of time a patient had had the disease, the age of the patient and his resistance to infection were factors bearing on possible recurrence. Cases of the so-called hemorrhagic type, in which severe hemorrhages occur, respond poorly and are prone to progress poorly. The functional end-result must not be lost sight of. Whereas in some of the cases classified only as "improved" undoubtedly the progress of the infection has been checked, yet strictures and diffuse narrowing of the colon, interfering materially with its powers of proper absorption and elimination, cause difficulty, although the patient's general condition may be excellent. Finally, it is still unfair to speak of "curing" chronic ulcerative colitis; "controlling" is the correct expression. As in many other devastating infections, patients are always obliged to do certain things for their future welfare. Therefore, it seems important that patients who have once overcome an attack of chronic ulcerative colitis should receive the vaccine periodically. Just

how often those periods of treatment should occur is still problematic, but progress in this direction is being made. Recently, with aging of the serum, and improvement in methods of precipitation, we have had more rapid response than in the cases reported in this paper. Enough time has not elapsed for the permanent value of the method to be known.

SUMMARY

The Fasting antibody solution obtained by precipitation in ether-water of the specific immune serum of chronic ulcerative colitis adds a new and valuable reagent to the armamentarium used in the treatment for bacterial chronic ulcerative colitis.

It is particularly efficacious in the treatment of the more severe, subacute cases in which ileostomy was formerly the treatment of choice.

This, in conjunction with the specific vaccine and other symptomatic agents, has greatly reduced the need of ileostomy.

Operation, and primarily ileostomy, has become limited to complications, with very few exceptions.

THE INFLUENCE OF AURICULAR CONTRACTION ON THE FIRST HEART SOUND AND THE RADIAL PULSE *

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The present-day clinical evaluation of heart sounds is unsatisfactory. The physical factors concerned in the production of the normal sounds, particularly the first sound, are imperfectly understood. Furthermore, little is known of the mechanisms by which modifications of these sounds are accomplished. It seemed possible, therefore, that studies of patients showing variations of the first heart sound in successive beats might be of interest. This report deals principally with certain of the effects of auricular contraction on the first sound. In this connection it became necessary to consider also the effect of auricular contraction on the amplitude of the pulse wave because of a possible relation between the intensity of the first heart sound and the ventricular output per beat. Wiggers [1] was able to furnish evidence to the effect that when the systolic discharge is increased the first sound is reduced in intensity.

INFLUENCE OF AURICULAR SYSTOLE ON THE FIRST HEART SOUND

It is well known that the intensity of the first heart sound as judged by auscultation may show phasic variation corresponding to the respiratory cycle or may be modified by disturbances in ventricular rhythm such as occur in auricular fibrillation and extrasystolic arrhythmia. In addition to these, however, there are striking variations associated with changes in the time relations of auricular and ventricular systoles.

These variations have received little attention. Griffith [2] described them in 1911 in two cases of heart block, being particularly impressed by the thumping, emphatic character of some of the beats, the quality of which he compared with that heard in mitral stenosis. In one case he was able to mark the position of the loud beats on a polygram, and he noted that they occurred when the auricles and ventricles contracted

* Submitted for publication, April 22, 1930.

* From the Edward Burton Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

1. Wiggers, C. J.: Factors Determining Relative Intensity of Heart Sounds in Different Auscultation Areas, Arch. Int. Med. **24**:471 (Nov.) 1919.

2. Griffith, T. W.: Remarks on Two Cases of Heart Block, Heart **3**:143 (Feb.) 1912.

at about the same time. He offered the suggestion that for the production of the loud sounds it may be necessary for the auricle to be in systole at the time the ventricle enters into contraction.

Lewis [3] stated that when auricular contraction slightly precedes the ventricular, intensification of the first heart sound occurs, but when the relation is reversed reduplication may result. He has published a heart sound record clearly illustrating these points. Lewis pointed out that such variation of the sounds is striking and may be heard in almost any case of dissociation. He regards the variation as a most valuable bedside test of complete heart block when instrumental aids are not available.

A few other observers have noted variations in the intensity of the first sound during heart block. Carter and Howland,[4] in a report on a child, aged 5 years, with congenital heart block, noted that the first heart sound was usually faint but from time to time a single beat was very loud. The marked accentuation of the sound was interpreted as due to synchronous systole of the auricles and ventricles. Harris [5] recently reported a case in which complete heart block had existed for at least twenty-eight years. In this patient inequalities of the first heart sound had been noted on the first record and were still present twenty-eight years later. Read [6] recently reported two cases of complete heart block in which inequalities of the first sound were noted.

We have confirmed Lewis' statement that inequalities of the first heart sound in A-V dissociation are frequently present, and that on auscultation of the heart, are striking enough to be of distinct value in the diagnosis of dissociated auriculoventricular beating. We have also found that the variations may be as striking in ventricular escape as in heart block. It is noteworthy that marked changes in the first sound tend to occur within the normal range of As-Vs time intervals, so that even in normally beating hearts the first sound may be modified according to the length of the interval.

Method.—The apparatus used for the recording of heart sounds consisted of a Western Electric electromagnetic contact transmitter,[7] a three-stage transformer coupled amplifier with an appropriate frequency-response characteristic, an electromagnetic diaphragm watch case type output receiver [7] and the Wiggers modification of the Frank segment capsule. This apparatus, which is very sensitive,

3. Lewis, T.: Lectures on the Heart, New York, Paul B. Hoeber, Inc., 1915, p. 66.

4. Carter, E. P., and Howland, J.: Occurrence of Congenital Atrioventricular Dissociation: Report of Case of Congenital Heart Block, Bull. Johns Hopkins Hosp. **31**:351 (Oct.) 1920.

5. Harris, K. E.: Notes on a Case of Complete Heart Block of Unusually Long Duration, Heart **14**:289 (March) 1929.

6. Read, J. M.: Complete Heart Block: Roentgen Kymographic Study, Arch. Int. Med. **45**:59 (Jan.) 1930.

7. Dodge, H. F.: The Stethophone, Electrical Communication, October, 1924, no. 2, vol. 3; Reprint B-105-1, Bell Telephone Laboratories.

was constructed for the purpose of studying the time relationships of heart sounds and murmurs. It causes slight distortion as well as magnification of the sounds, as judged by comparison of auscultatory observations directly over the heart and at the output receiver, but we were able to demonstrate, by signalling on tracings, that relative intensities of beats as judged by the stethoscope correspond to variations of the amplitude of the waves recorded (fig. 4). The Wiggers recorder was controlled by phonocardiograms and found to be accurate when care was taken to use sufficiently light reflecting mirrors. Tuning fork vibrations were faithfully recorded up to and including 512 vibrations per second.

Electrocardiograms and sound tracings were recorded on the same strip, parallax being avoided.

Case 1.—G. L., a white man, aged 49, had been under our observation for one and one-half years. During his first admission to the hospital he had intermittent heart block,[8] but subsequently the block remained complete. There was a history of acute arthritis (possibly rheumatic fever) at the age of 24 and again at 41. No other etiologic factor for the block was discoverable except possibly

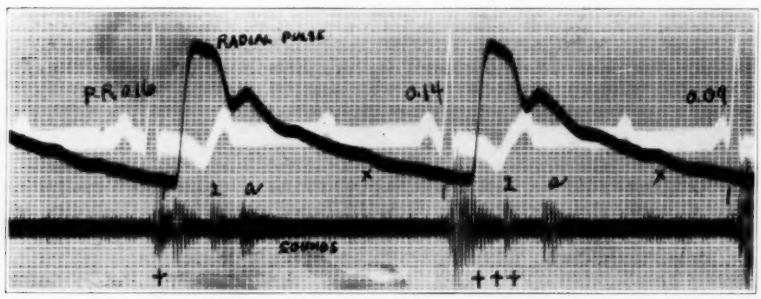


Figure 1—Left

Fig. 1 (case 1).—Complete heart block. Change of intensity of the first heart sound as the P-R interval shortens. The number of plus marks in this and subsequent tracings indicates the arbitrary classification of sounds according to intensity. The first auricular beat during each ventricular diastole is followed by a murmur (*a*). The sounds are imperfectly recorded because of the presence

some infected roots of teeth which had been extracted before admission. The heart was found by orthodiagram to show moderate generalized enlargement. There was a systolic apical murmur. During the presence of complete heart block, two striking auscultatory observations presented themselves. There was decided variation in the intensity of the first heart sound independent of respiratory excursions, and in addition short murmurs were heard having a rate of from 80 to 90 per minute, which could be timed with a venous wave in the neck. The murmurs were readily shown by tracings to be related to auricular activity (fig. 11).

In figure 1 are shown samples of tracings, indicating the variations in amplitude of the sound vibrations recorded. These changes in ampli-

8. Sudden transitions occurred from normal mechanism to incomplete or complete block. All sequential beats, even during incomplete block, had normal P-R intervals.

tude are not to be regarded as quantitative, but they may be accepted as a rough index of the relative intensity of sounds as judged by auscultation with a stethoscope.

In the accompanying table we have compared the time relationships of the auricular and ventricular beats to the intensity of the first heart sound as indicated by the amplitude of recorded vibrations. The table indicates that first sounds of greatest intensity are recorded when auricular systoles slightly precede ventricular, especially within the P-R range from 0.04 to 0.13 second.[9] With minor discrepancies, sounds of medium intensity occur on either side of this zone, the limits being a P-R interval of 0.20 second and a R-P interval of 0.03 second. All ventricular systoles failing to have an auricular systole within this range produce faint first sounds.

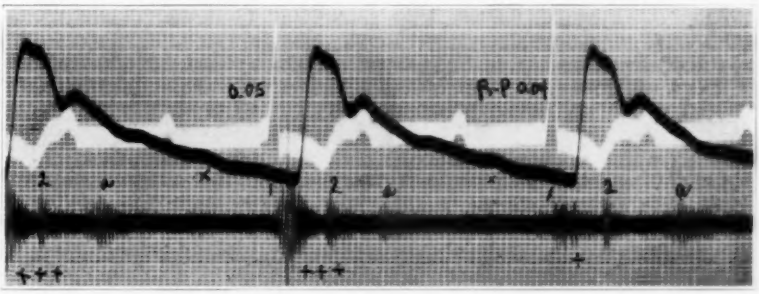


Figure 1—Right

of a constant vibration with a frequency of 175 in the apparatus. That the changes in the first sound are significant is shown by the remarkable constancy of the recorded second sounds as well as the inequalities noted on auscultation. The pulse waves show no significant variations. The points marked *x* show waves due to auricular contraction.

The foregoing relationships are shown graphically in figure 2. The minor discrepancies noted are at least in part attributable to respiratory movement (variable relation of the heart to the wall of the chest) and also to errors in technic, such as variations in pressure on the receiver.

CASE 2.—A. S.,[10] a white woman, aged 53, had intermittent heart block over a period of at least five years, possibly much longer. When the block was complete, marked differences in the intensity of the first heart sound were noted which

9. Our use of the designations P-R and R-P measurements of intervals in this paper does not include the usual connotation of transmission of the impulse. It refers merely to the relative positions of auricular and ventricular systoles as they were measured on electrocardiograms.

10. The clinical data for this patient (case 3) were reported fully by one of us (C. C. W.) and T. M. McMillan (Observations on the Mechanism of Relatively Short Intervals in Ventriculo-Auricular and Auriculoventricular Sequential Beats During High Grade Heart Block, Am. Heart J. **4**:521, 1929).

*Comparison of Time Relationships of the Auricular and Ventricular Beats with the Intensity of the First Heart Sound**

Duration of P-R or R-P Intervals in Seconds		Relative Intensity of Sounds							Height of Recorded Radial Pulse Waves in Millimeters		
		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	First Strip, Case 1	Second Strip, Case 1	Case 8
R-P	0.28	..	..	..	..	..	..	+	....	....	....
	0.25	..	..	..	..	..	..	+	....	....	....
	0.20	..	..	..	..	..	..	+	....	....	....
	0.15	..	..	..	..	..	..	+	....	....	....
	0.14	..	..	..	..	..	..	+	....	....	....
	0.12	..	+	..	..	..	..	..	....	....	....
	0.10	..	..	..	..	..	+	..	....	....	....
	0.10	+	..	..	..	..	..	..	....	....	....
	0.08	+	..	..	..	..	++	..	....	....	....
	0.08	..	..	..	..	..	++	+	....	....	....
	0.07	..	..	..	..	..	++	..	....	....	....
	0.06	..	..	+	..	..	..	..	....	....	....
	0.05	..	++	..	..	..	..	..	....	....	....
	0.04	+	++	+	..	..	..	..	....	....	....
	0.03	++	++	++	..	..	..	+	....	....	....
	0.03	..	..	..	..	..	..	+	....	....	....
	0.02	..	++	++	..	..	..	+	....	....	....
	0.01	+	++	..	..	..	..	+	....	....	....
	0.00	++	+++	..	+++	..	..	+	....	34.5	....
	0.00	..	..	..	++	..	..	+	....	35.0	....
P-R	0.01	.	..	..	+++	..	..	+	....	....	....
	0.02	+++	+++	++	..	..	..	..	....	....	....
	0.02	++	..	..	..	..	..	..	....	....	....
	0.02	++	..	..	..	..	..	..	....	....	....
	0.03	++	..	..	+++	..	..	..	....	35.0	....
	0.04	+++	+++	+++	..	..	+++	+	35.0	....	21.5
	0.04	..	..	..	..	..	+++	..	35.0	....	22.0
	0.05	..	..	++	..	..	..	+	35.0	....	....
	0.06	..	+++	..	+++	..	+++	..	....	....	....
	0.06	..	..	..	..	..	++	..	....	....	21.5
	0.07	+++	+++	..	..	..	..	..	....	....	21.5
	0.07	..	+++	..	+++	..	..	+	35.0	....	21.5
	0.07	..	..	..	..	..	..	..	....	....	22.0
	0.07	..	..	..	..	..	..	..	....	....	22.5
	0.07	..	..	..	..	..	.	..	....	....	22.5
	0.08	+++	..	+++	+++	..	..	++	....	....	22.0
	0.08	..	..	+++	..	..	..	..	....	....	....
	0.08	..	..	+++	..	..	..	..	....	....	....
	0.08	..	..	++	..	..	..	..	....	....	....
	0.09	..	+++	..	..	..	..	..	....	....	....
	0.10	+++	+++	+++	+++	..	+++	..	36.0	....	23.5
	0.10	+++	..	..	..	..	++	..	....	....	....
	0.11	+++	..	..	+++	..	++	++	37.0	....	24.0
	0.11	+++	..	..	..	..	..	..	37.0	....	....
	0.12	..	..	+++	+++	..	+++	..	....	41.0	....
	0.12	..	..	+++	..	..	..	..	....	....	....
	0.13	..	..	+++	+++	..	+++	++	....	41.0	25.0
	0.13	..	..	..	..	..	+++	..	....	....	25.0
	0.14	++	..	..	+++	..	++	++	38.5	....	26.5
	0.14	..	..	..	+++	..	++	++	39.0	....	....
	0.14	..	..	..	++	..	..	..	....	....	....
	0.15	..	+++	..	..	..	..	..	....	....	....
	0.15	..	..	..	++	..	..	..	39.5	41.0	24.5
	0.16	++	..	+++	+++	..	+++	++	39.5	....	26.5
	0.16	++	..	..	++	..	++	++	....	....	27.0
	0.16	..	..	..	+	..	..	++	....	....	....
	0.16	..	..	..	..	..	..	++	....	....	....
	0.16	..	..	..	..	..	..	+++	....	....	....
	0.17	..	++	+++	..	..	++	+++	....	....	....
	0.17	..	..	..	..	..	++	+++	....	....	....
	0.17	..	..	..	..	..	..	++	....	....	....
	0.18	..	++	+++	++	..	.	..	....	....	....
	0.18	..	..	+++	+	..	..	..	....	....	....
	0.18	..	..	+++	..	..	..	..	....	....	....
	0.18	..	..	+++	..	..	..	..	....	....	....
	0.19	++	+	..	..	..	..	+++	....	....	26.5
	0.19	..	+	..	..	..	..	+++	....	....	....
	0.20	++	..	+++	..	..	+	+++	....	41.5	....
	0.20	..	..	++	..	..	..	+++	....	....	....
	0.20	..	..	++	..	..	..	+++	....	....	....
	0.21	..	..	..	..	..	..	..	39.0	41.0	....
	0.21	..	..	..	..	..	..	..	39.5	42.5	....
	0.21	..	..	..	..	..	..	..	39.5	....	....
	0.22	+	..	++	..	..	..	..	....	....	....
	0.22	..	..	++	..	..	+	..	....	41.5	28.0

* The data tabulated in each column, except that under case 5, were obtained from a representative continuous strip of tracing. In case 5 the data were obtained from three tracings. The material is arranged according to the lengths of R-P and P-R intervals (first column) measured on the electrocardiograms. The relative intensity of sounds was arbitrarily classified according to the amplitude of the recorded sound waves, + indicating tracings with waves of low amplitude; ++, waves of intermediate amplitude, and +++, waves with the greatest amplitude. The height of the radial pulse waves was measured on the tracings.

Comparison of Time Relationships of the Auricular and Ventricular Beats with the Intensity of the First Heart Sound—Continued*

Duration of P-R or R-P Intervals in Seconds		Relative Intensity of Sounds							Height of Recorded Radial Pulse Waves in Millimeters		
		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	First Strip, Case 1	Second Strip, Case 1	Case 8
P-R	0.23	..	+	..	..	..	+	+++	....	....	24.5
	0.24	..	..	++	+	+	+	..	40.5	42.0	....
	0.24	..	..	+	..	+	..	..	....	....	....
	0.25	..	+	+	+	+	+	..	38.5	40.0	25.5
	0.26	+	+	+	..	+	..	..	40.0	....	....
	0.26	..	+	..	..	+	..	..	38.5	....	....
	0.26	..	+	..	..	+	..	..	38.5	....	....
	0.27	..	..	+	..	..	..	..	....	....	....
	0.27	..	..	+	..	..	..	..	....	....	....
	0.28	+	..	..	..	..	..	..	38.0	....	....
	0.28	..	..	..	..	..	..	..	38.5	....	27.0
	0.29	..	+	..	..	+	..	..	....	....	....
	0.30	..	+	..	..	..	..	..	38.0	40.0	25.0
	0.30	..	..	..	..	..	..	..	39.0	....	....
	0.31	..	+	..	..	..	..	..	38.0	41.0	....
	0.32	+	+	..	+	..	..	..	....	....	....
	0.32	..	..	..	+	..	..	..	....	....	....
	0.32	..	..	..	+	++	..	..	....	....	....
	0.33	..	+	..	+	++	..	..	....	....	26.0
	0.33	..	+	..	+	++	..	..	....	....	26.5
	0.34	+	..	..	+	++	..	..	....	....	25.0
	0.34	..	..	..	+	++	..	..	....	....	....
	0.34	..	..	..	+	++	..	..	....	....	....
	0.35	..	..	..	..	..	..	..	37.0	....	25.0
	0.35	..	..	..	..	..	..	..	37.5	....	....
	0.36	..	+	..	+	..	..	..	37.5	39.0	27.5
	0.36	..	+	..	..	..	..	..	39.0	38.5	26.5
	0.37	+	+	..	..	..	..	..	37.0	....	....
	0.37	..	..	..	..	..	..	..	36.5	....	....
	0.38	..	..	+	+	+	..	..	37.5	....	27.0
	0.38	..	..	..	..	+	..	..	....	....	25.0
	0.39	+	..	..	++	+	..	..	36.5	36.5	26.0
	0.39	..	..	..	..	+	..	..	....	36.5	....
	0.39	..	..	..	..	+	..	..	....	36.5	....
	0.40	..	+	..	+	+	..	..	....	....	....
	0.41	..	+	..	..	+	..	..	....	....	24.5
	0.42	..	+	..	..	..	..	..	....	38.5	27.0
	0.43	..	..	..	..	..	..	..	....	....	....
	0.44	..	+	+	..	..	..	..	....	36.5	....
	0.44	..	..	+	..	..	..	..	....	....	....
	0.45	..	+	..	..	..	..	..	....	34.5	....
	0.46	+	..	..	..	..	..	..	....	38.0	....
	0.47	..	..	..	..	..	..	..	....	....	....
	0.48	+	..	..	+	..	..	..	36.0	36.5	....
	0.48	..	..	..	..	..	..	..	36.5	....	....
	0.48	..	..	..	..	..	..	..	38.0	....	....
	0.49	..	..	..	..	..	..	..	35.5	33.0	....
	0.49	..	..	..	..	..	..	..	38.0	....	....
	0.50	+	..	..	..	..	..	..	37.0	....	24.0
	0.50	..	..	..	..	..	..	..	....	....	23.5
	0.50	..	..	..	..	..	..	..	....	....	23.0
	0.51	..	..	..	..	..	..	..	....	....	....
	0.52	..	..	..	+	..	..	..	35.5	....	....
	0.53	..	+	..	..	..	..	..	36.0	36.5	....
	0.53	..	..	..	..	..	..	..	36.0	....	....
	0.54	..	+	..	..	..	..	..	37.0	....	....
	0.55	..	..	..	+	..	..	..	....	33.0	....
	0.56	+	..	..	..	..	..	..	....	....	....
	0.57	..	..	..	..	..	..	..	35.5	....	....
	0.58	..	..	..	..	..	..	..	....	....	....
	0.59	+	..	..	..	..	..	..	35.5	....	....
	0.60	..	..	..	+	..	..	..	....	....	26.0
	0.60	..	..	..	+	..	..	..	....	....	....
	0.61	..	..	..	+	..	..	..	....	....	....
	0.62	+	..	..	+	..	..	..	35.0	....	23.0
	0.62	..	..	..	..	..	..	..	35.0	....	....
	0.63	..	..	..	..	..	..	..	....	....	....
	0.64	+	..	..	+	..	..	..	35.5	....	....
	0.65	..	..	..	+	..	..	..	....	....	....
	0.66	..	..	..	..	..	..	..	....	....	....
	0.67	..	..	..	..	..	..	..	....	....	25.0
	0.68	..	..	..	..	..	..	..	....	....	24.5
	0.68	..	..	..	..	..	..	..	....	....	24.0
	0.69	..	..	..	..	..	..	..	....	....	23.0
	0.70	..	..	..	..	..	..	..	....	....	....
	0.71	..	..	..	..	..	..	..	....	....	....
	0.72	..	..	..	+	..	..	..	....	....	....
	0.73	..	..	..	+	..	..	..	....	....	....
	0.74	..	..	..	..	..	..	..	....	....	....
	0.75	..	..	..	+	..	..	..	....	....	....
	0.76	..	..	..	..	..	..	..	....	....	....
	0.83	..	..	..	..	..	..	..	....	....	22.0

were not attributable to respiration. There was a variable systolic murmur, and in addition faint sounds were heard corresponding to auricular beats. Eventually, a very slow idioventricular rate developed, and the patient died. At necropsy, the heart was found within normal limits of size, although there were patchy arteriosclerosis and fibrosis of the myocardium, including particularly the junctional tissues. There was no valvular disease.

In this patient the heart sounds were recorded according to the technic developed by Wiggers, except that a Bowles stethoscope was used as transmitter. No amplification was employed. It is of interest that within the normal range of

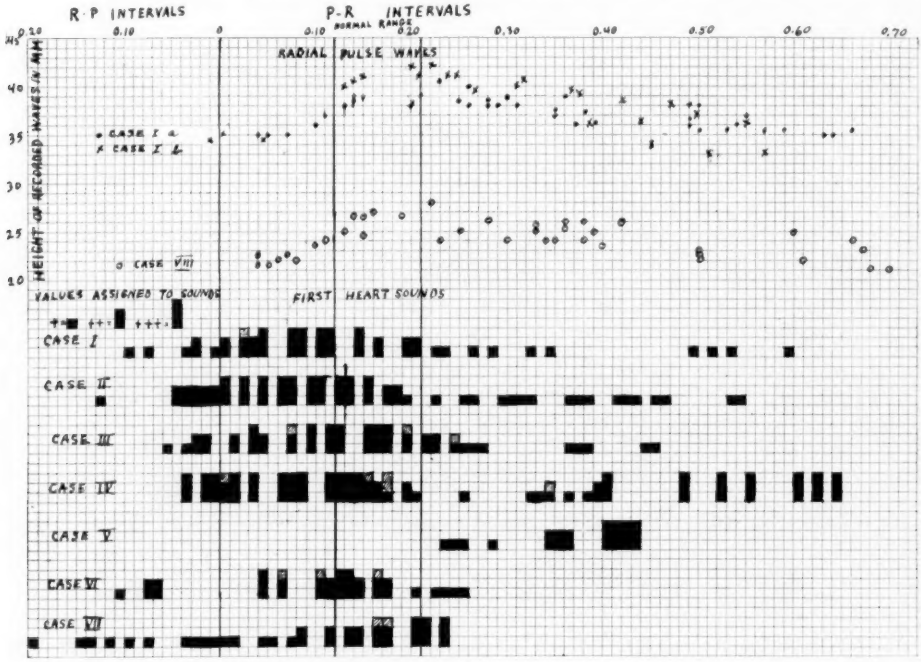


Fig. 2.—The data charted in each instance, except under case 5, were obtained from a representative continuous strip of tracing. The values plotted for the radial pulse waves were obtained by measurements of the height of excursion from the beginning of the upstroke to the peak of the wave. The first heart sounds were arbitrarily divided into three groups according to the relative intensity, as judged from the amplitude of the sound waves. For purposes of charting, a single black square indicates a relatively weak first sound, a vertical column of 3 squares a relatively loud sound, and a column of 2 squares an intermediate sound. Hatching of the column indicates the extent of variability recorded for the P-R interval charted.

P-R intervals the intensity shifted rapidly from loud to faint as the P-R time lengthened. This patient also showed a moderate increase in the sounds when the ventricular beat preceded the auricular by a very short interval. The relationships of varying intensity of sounds to auriculoventricular time intervals are thus similar to those recorded in case 1 (fig. 3 and table).

Case 3.—Mrs. S. H., aged 65, had been under observation for five years. She complained of palpitation, dyspnea on exertion, headache and weakness. The heart was moderately enlarged to the left, and there was a systolic murmur at the aortic area. The blood pressure had been consistently high, the systolic readings varying between 190 and 290 mm. of mercury. Four years before examination, high grade heart block developed.[11] In July, 1927 (before our attention was attracted to this subject), a note was made on her record that the heart sounds varied in strength.

The variations in the intensity of the first heart sound were the most marked that we have encountered. The faint sounds were heard with difficulty by stethoscope and could scarcely be recorded. The loudest sounds, on the other hand, had an intensity that might properly be classified as normal or average, and the amplitude of the sound vibrations recorded were up to the average that we have obtained by this technic in normal persons (fig. 4).

Sounds of greatest intensity were recorded when the P-R intervals fell in the zone of from 0.08 to 0.20 second. On either side of this zone, there were narrow zones (R-P 0.03 to P-R 0.05 and P-R 0.20 to P-R 0.24) during which sounds of intermediate intensity were recorded. As in almost all of our records, there tended to be some overlapping at the margins (table and fig. 2). When the P-R intervals had a duration of from 0.24 to 0.68 second, the sounds were very faint.

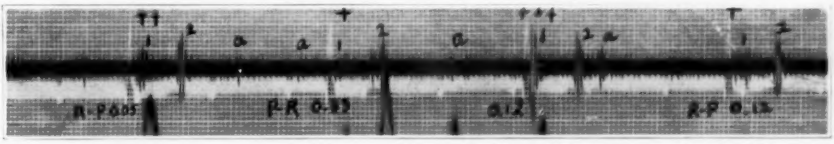


Fig. 3 (case 2).—Complete heart block. Inequalities of the first sound associated with changes of P-R intervals. They were recorded without amplification, according to the technic described by Wiggers, except that a Bowles stethoscope was used as a transmitter.

Case 4.—F. D., aged 6 years, was a fairly well grown, healthy-looking girl. A marked bradycardia had recently been discovered by accident. Its duration was not known, since it had caused no symptoms, and no previous examination of the heart had been made. An electrocardiogram showed complete heart block with an auricular rate of 82 and a ventricular rate of 46. By orthodiagram the heart revealed a slight generalized enlargement. There was a systolic murmur at the apex. No diastolic murmur could be heard. Decided variations in the intensity of the first sound were noted.

Comparison of the electrocardiogram and sound tracing (fig. 5) revealed the following: The sounds were comparatively faint when the P-R measurements had a range of from approximately 0.18 to 0.34 second. On either side of this zone (P-R intervals of from 0.14 to 0.18 second and from 0.34 to 0.39 second) the sounds tended to have moderate intensity although some variations were noted. In all other relationships of auricular and ventricular beats recorded, the first

11. The heart block has never been quite complete. Auricular beats falling within a certain time zone following ventricular beats were transmitted, causing some ventricular irregularity. The mechanism bears some resemblance to what has been described as the supernormal phase of conduction, and this feature of the case will be reported later.

sounds had maximum intensity (table and fig. 2). The variations of intensity were therefore similar to those of cases 1, 2 and 3 in the short range of P-R intervals, but differed as the P-R intervals increased beyond 0.34 second.

Case 5.—P. N., an unusually well developed boy, aged 14 years, was seen by Dr. T. Grier Miller during the course of an attack of acute tonsillitis. Dr. Miller reported to us that he was impressed by finding a pulse rate of 60 despite a temperature of from 102 to 103 F. and by the fact that marked differences of intensity in the first heart sound were present, although the rhythm was quite regular. On the basis of these observations we ventured the opinion that the boy had complete heart block. Three days later he was brought to the hospital. At that time the rhythm was irregular, and an electrocardiogram showed incomplete block (fig. 6, top strip). The assumption of a complete block having been present a few days before is therefore not without reason.

The sound tracings showed decided inequalities of the first sound. In the top strip these might be attributed to the ventricular irregularity but strips 2 and 3, which were registered on subsequent days but from the same point on the chest, and which show comparable intensities of the second sound, indicate rather clearly that the sounds are related to the duration of the P-R intervals. In this con-

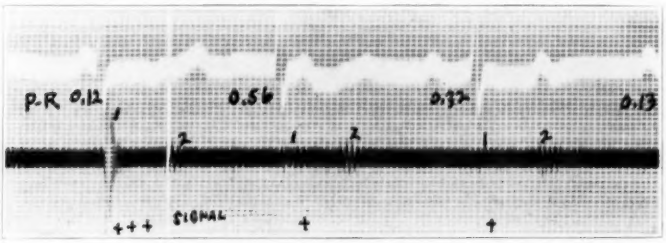


Figure 4—Left

Fig. 4 (case 3).—High grade, almost complete heart block. Variations in first heart sounds corresponding to changes in P-R intervals. The loudest beats,

nection it is of interest that although observations of P-R intervals over a wide range were not available, the intensity of the first sound increased as the P-R intervals lengthened from 0.24 to 0.37 second, thus resembling the changes recorded in case 4 but differing from those in cases 1, 2 and 3 (fig. 2).

Case 6.—C. M., a married woman, aged 32, had been under observation in the cardiovascular section for fourteen months. She complained of faintness on exertion, doubtless due to the fact that exercise produced attacks of paroxysmal ventricular tachycardia. At other times, tracings showed a minor defect in A-V conduction, and ventricular escape was frequently present. When the auricular-ventricular relationships remained constant (sequential beats with P-R intervals of 0.28 second) the sounds were faint, and no marked variations in the intensity of the first sound were discoverable (fig. 7). During ventricular escape, however, marked variations were present which were readily detected by stethoscope and also by examination of the sound records.

The sounds tended to have the greatest intensity when the P-R measurements ranged from 0.04 to 0.13 second (table and fig. 2). When the P-R intervals were from 0.14 to 0.17 second, the sounds were of moderate intensity, and from

0.20 to 0.25 they were comparatively faint. It is also of interest that three beats with R-P intervals of 0.08, 0.08 and 0.17 second caused sounds of moderate intensity but one with a R-P interval of 0.11 was faint. Thus in the range of auriculoventricular relationships during which observations could be made the variations of sound intensity were similar to those of cases 1 to 4, inclusive.

CASE 7.—L. G., an unmarried woman, aged 29, was referred for study by the thyroid section to the cardiovascular section. A subtotal thyroidectomy had been performed two years previously. This operation had apparently completely relieved the hyperthyroidism from which she had been suffering; nevertheless, she had not completely regained her strength. Our observations included a decidedly enlarged heart, aortic regurgitation and mitral stenosis. The valvular disease was probably of rheumatic origin, although there was no history of rheumatic fever. The blood pressure was 130 systolic and 60 diastolic. There were no congestive phenomena but the margin of cardiac reserve was narrow.

It was possible to make only one examination of this patient. Our attention was attracted by a slight arrhythmia and on auscultation by marked variations in the intensity of the first heart sounds. These variations are shown in figure 8, figure 2 and the table. Vibrations of greatest amplitude were recorded when the

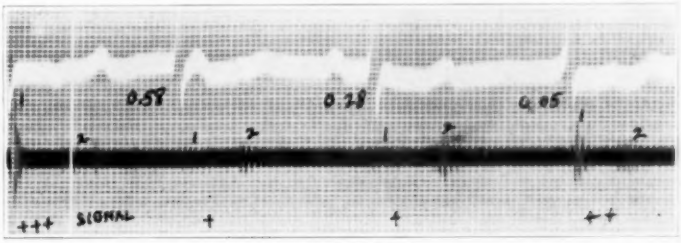


Figure 4—Right

as judged by auscultation, were signalled on the tracing (vertical broad white lines).

P-R measurements were from 0.16 to 0.23 second. In the zone of P-R measurements ranging from 0.08 to 0.16 second the sounds were of moderate intensity, while from 0 to 0.07 the sounds were relatively faint. All beats the ventricular systole of which preceded auricular systole had relatively faint first sounds.

In this patient the relationships of change in sound intensity to auriculoventricular intervals were different from those observed in other cases. Instead of diminishing intensity as the P-R interval increased in the normal range, the sounds tended to become louder. In this connection it should be pointed out that this is the only patient in the series in whom mitral stenosis was detected.

INFLUENCE ON AMPLITUDE OF THE RADIAL PULSE WAVE

In view of the marked differences in the first heart sound recorded in case 1, it seemed worth while to make records of the radial pulse wave in order to discover whether any differences in amplitude of pulse

waves might be found to correspond with the variations in the intensity of the first sound. Read [6] recently found differences in the shape of the waves of left ventricular excursion (roentgenograms) during complete heart block, which he attributed to variations in the number of auricular systoles during ventricular diastole. In addition, he surmised that inequalities of the first heart sound at successive systoles suggest a variability of stroke volume. This point will be referred to later. As far as we are aware, however, there is no actual evidence to be found in the literature suggesting a correlation between the intensity of the first heart sound and the amplitude of the pulse wave, except that reported by Wiggers.[1]

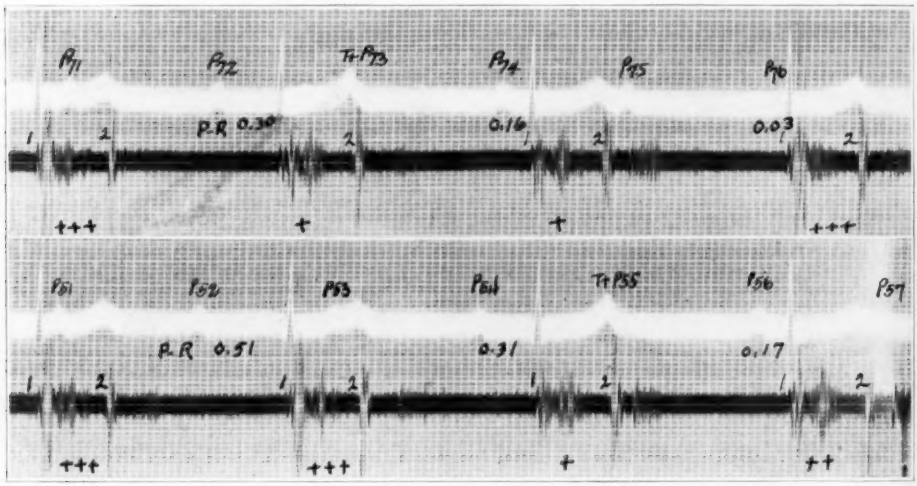


Fig. 5 (case 4).—Complete heart block. Variations in the first heart sounds and their relations to the length of the P-R intervals.

The experiments of Gesell [12] indicate the possibility that there might be a relationship between the duration of P-R intervals and the amplitude of pulse waves. It has been found by several investigators that auricular systole is capable of increasing ventricular output over that maintained by venous pressure alone, but Gesell discovered in addition that auricular systole varied in effectiveness in increasing ventricular output, depending on the time relation of auricular systole to ventricular

12. Gesell, R. A.: Auricular Systole and Its Relation to Ventricular Output, Am. J. Physiol. **29**:32 (Nov.) 1911; Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation and Stimulation of the Vagus Nerve, ibid. **40**:267 (April) 1916.

systole. He found that auricular systoles completed from 0.008 to 0.02 second before ventricular systole is begun seem to have the greatest effect, although even those auricular systoles partly "stoppered" by ventricular systole have a positive effect on the filling of the ventricles. Auricular systoles occurring entirely within ventricular systole have no effect, while those occurring in ventricular diastole increase in effectiveness from nothing to maximum as they approach the beginning of ventricular systole.

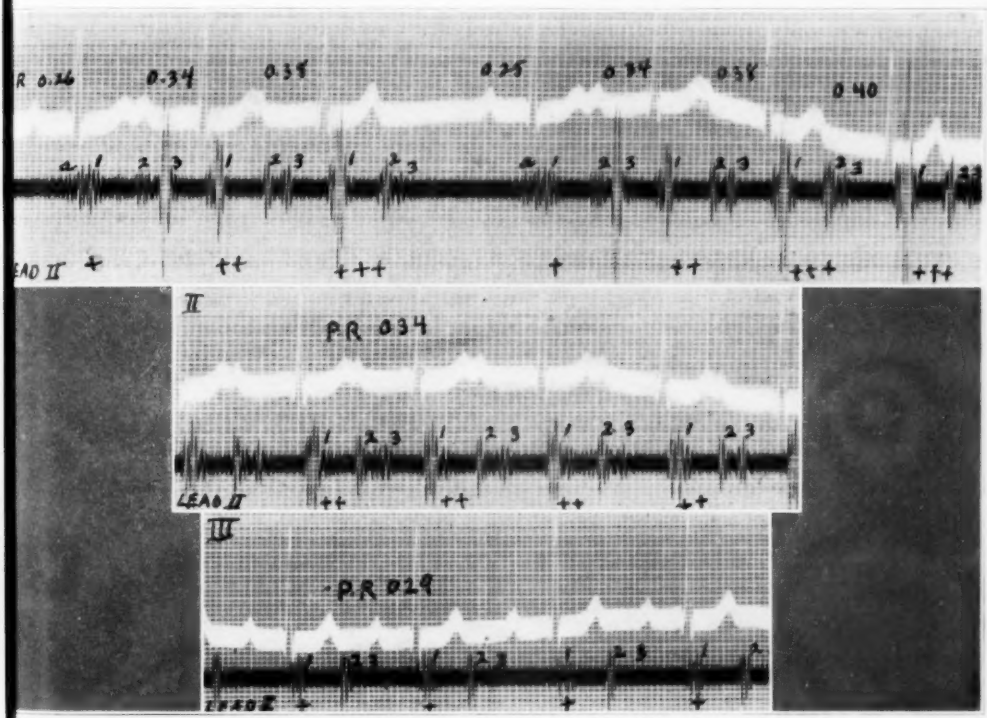


Fig. 6 (case 5).—The top strip shows incomplete heart block. The lower strips, which were made on subsequent days, show prolongation of P-R intervals but no dropped beats. Marked variations in the first sound are recorded in the top strip. In strip II, in which the P-R intervals have a duration of 0.34 second, the first sound is comparable with those beats in strip I having a P-R interval of approximately 0.34 second. In strip III with P-R intervals of 0.29 second the first sound is comparable with the beats in strip I having a P-R interval of from 0.25 to 0.26 second. There are also extraordinary changes in the third heart sound depending on the relation of the auricular contraction to the end of the ventricular systole.

In this connection it is of interest to note that Griffith [2] described pulsus alternans in a patient with high grade heart block and slow ventricular rate. There was from 3 to 2 block with the auricular systoles so placed that every second ventricular beat quickly followed auricular contraction. This relationship was associated with the larger pulse waves. The alternate ventricular systoles were not immediately preceded by auricular beats, but the two occurred practically simultaneously. Under these circumstances, smaller pulse waves might be due to the time relations of auricular and ventricular systoles.

Method.—An ordinary pulse-recording tambour from the Jaquet polygraph was strapped about the wrist with the button placed over the radial artery. The

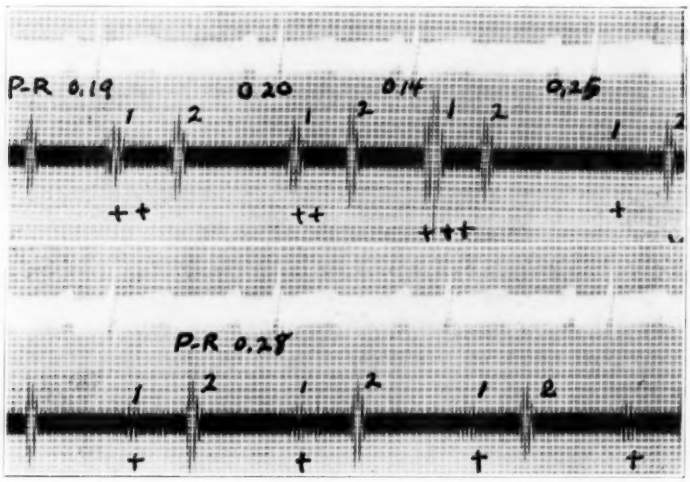


Fig. 7 (case 6).—Ventricular escape. Marked variations of intensity of the first sound are present, depending on the duration of the P-R interval. When the rhythm is regular and the P-R intervals are prolonged (lower strip), the sounds are uniformly faint.

tambour was connected by a rubber tube with the Wiggers modification of the Frank segment capsule. Simultaneous electrocardiograms and pulse curves were made, and in some tracings sound records were included. In the tracing that includes electrocardiograms, pulse waves and sound vibrations, the arrangement of mirrors was such that slight parallax was present. This has no bearing on our observations.

In case 1 the pulse wave tracings showed marked differences in their duration (from the beginning of the upstroke to the dicrotic notch) and shape (fig. 9). The waves of greatest amplitude tended to be the longest. The variations in the pulse waves were found to bear

a definite relationship to the duration of the intervals between ventricular systole and the preceding auricular systole (table and fig. 2). When these intervals were very short (less than 0.1 second), smaller pulse waves were recorded. Between 0.10 and 0.13 second, increase in size of pulse waves occurred. The optimum P-R range was approximately from 0.12 to 0.31 second, after which a gradual decline in amplitude of pulse occurred.

Numerous pulse tracings were made of this patient, and all but two showed the type of variation described with similar relations to the P-R intervals. The comparative magnitude of the variations differed from day to day. In the two exceptional tracings no significant variations in amplitude were discoverable (see pulse tracing, fig. 1).

Pulse tracings were also made in cases 3, 4 and 6. In case 4, no significant variations in amplitude were recorded. The pulse waves in cases 3 and 6 were more difficult to analyze because of ventricular

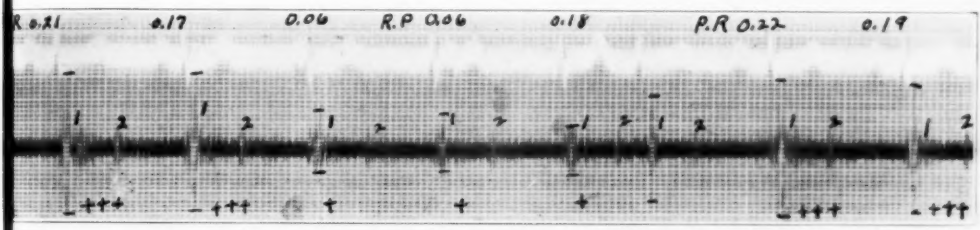


Fig. 8 (case 7).—Ventricular escape. Marked variations of intensity of first sound depending on the duration of the P-R intervals. The usual relations are reversed, possibly due to the presence of mitral stenosis.

irregularity. After a careful study of these tracings, we were unable to make out any significant relation to the duration of P-R intervals.

Case 8.—R. W., a married woman, aged 35, had had complete heart block for nine years. The etiology of this condition was uncertain. The heart was only slightly enlarged, and there was a fairly distinct systolic apical murmur. By auscultation decided differences in the intensity of the first heart sound were easily detected, but unfortunately, owing to temporary trouble with the apparatus, satisfactory sound tracings were not obtained.

A sample of radial pulse tracing is shown in figure 10. The amplitude of the waves in relation to the length of P-R intervals is given in the accompanying table and is shown graphically in figure 2. Minor variations in amplitude independent of the duration of P-R intervals were also recorded. Nevertheless, the table and figure 2 show a distinct influence of P-R intervals on the amplitude of the waves. When the P-R intervals were below 0.10 second, the pulse waves had the smallest amplitude. The amplitude increased as the P-R interval lengthened. The largest pulse waves were recorded in a range of approximately from 0.14 to 0.42 second. Beyond 0.42 second a decline in the height of the pulse waves appeared to begin, although unfortunately the observations are too few in

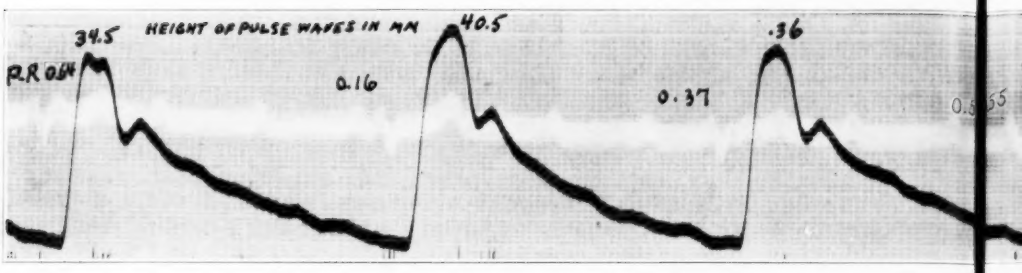


Fig. 9 (case 1).—The relation between the size of

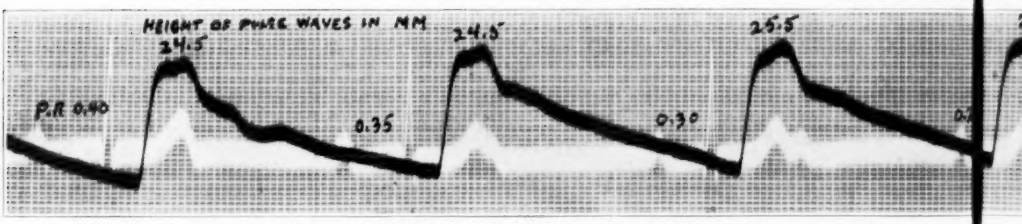


Fig. 10 (case 8).—The relation between the size of

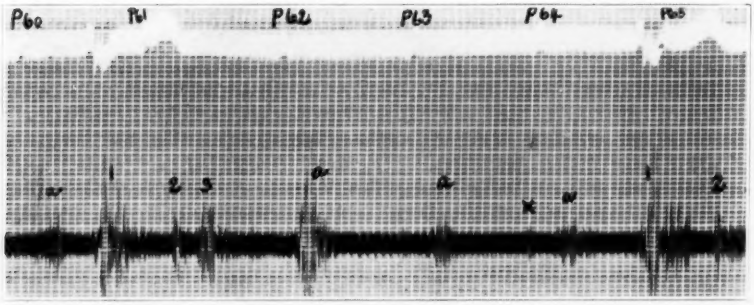
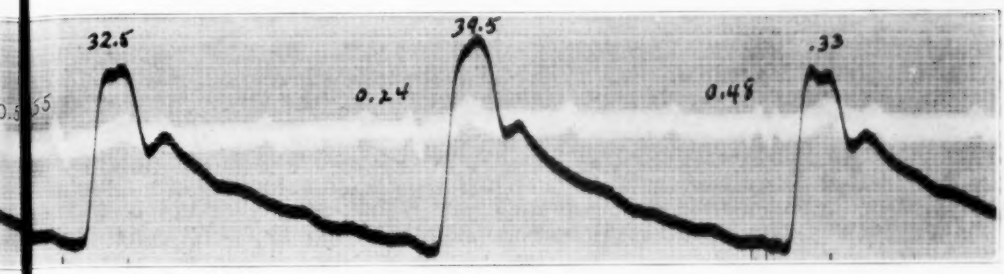
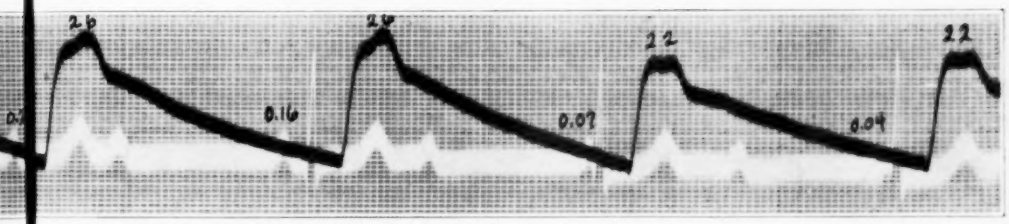


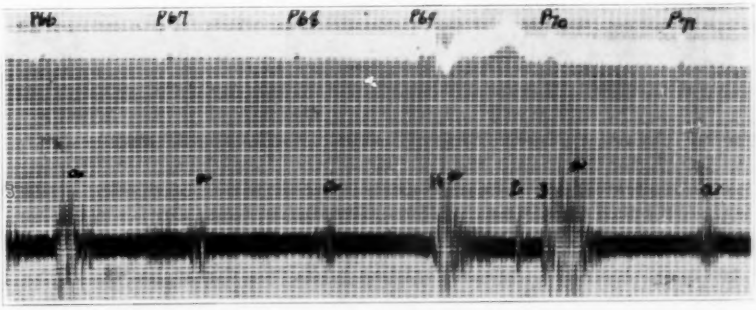
Fig. 11 (case 1).—The tracing shows a murmur following each P wave. those in late diastole. When this murmur coincides with the third heart sound,



of these waves recorded and the duration of the P-R intervals.



of these waves recorded and the duration of the P-R intervals.



Those falling in early ventricular diastole are louder and more prolonged than a very loud and prolonged murmur occurs.

this area to permit detailed analysis. The trend in the amplitude of the pulse waves continued downward as the P-R interval lengthened. It was of interest that higher pulse waves were recorded when the P-R interval was as long as 0.6 second than when it was under 0.1 second.

The curve of pulse amplitude in its relation to the duration of the P-R interval is in general similar to those obtained in case 1. The time relationships of the increase in amplitude of pulses are practically identical in the two cases, but the downward slope is more gradual in case 8.

COMMENT

Variations in Pulse Waves.—After having recorded in case 1 definite variations in the amplitude of pulse waves, and observed the relation of these variations to the duration of P-R intervals, we anticipated that similar observations might be frequent in cases with dissociated beating of the auricles and ventricles. We observed them, however, in only one of four other cases. Furthermore, even in case 1, in which the opportunity was afforded for making many tracings, at least two curves showed no significant differences in the amplitude of the pulse waves. It is possible that had we been able to repeat the studies more often in the other patients, we might have recorded variations.

The lack of consistency in the range of pulse wave variations from day to day, despite the insignificant changes in either auricular or ventricular rates, suggested that some factor that we failed to recognize was operative. Possibly, this factor may have been the height of venous pressure, by which, according to Henderson and Barringer,[13] it is determined whether or not auricular systole has any appreciable influence on ventricular filling.

The work of Gesell [12] probably furnishes the best clue to the variations in amplitude of pulse waves. He brought forward evidence for the view that increased ventricular output resulting from auricular systole is the result of such factors as increased initial tension of the ventricles, lengthening of the fibers and altered surface volume relation.

Our studies could not be expected to yield any direct evidence bearing on this point; nevertheless, an accidental observation in case 1 seems to deserve mention. It was stated in the protocol of case 1 that short murmurs were heard corresponding to the auricular beats (fig. 11). The distinctness of these murmurs varied according to their position in ventricular diastole; those occurring early were easily heard and recorded while those occurring in the latter part were less distinct and frequently could not be recorded. The murmurs that were readily recorded began from 0.14 to 0.16 second after the beginning of the P-wave and persisted approximately from 0.10 to 0.16 second. We may

13. Henderson, T., and Barringer, T. B., Jr.: The Relation of Venous Pressure to Cardiac Efficiency, Am. J. Physiol. **31**:352 (March) 1913.

assume that these murmurs represent vibrations produced by the blood flow from the auricles to the ventricles following an auricular beat.[14] Their time incidence is in a zone approximately from 0.14 to 0.30 second after the beginning of the P wave. This zone corresponds to the period during which the largest pulse waves are present. Physiologic evidence supports the view that both initial intraventricular tension and ventricular content (which determines the length of the fibers and the altered surface volume relation) are factors of importance in the efficiency of the heart beat. If only ventricular content were concerned, pulse waves would be expected to continue to increase in size as ventricular systole fell later in the period of active flow from the auricles to the ventricles; this, however, was not the case, as the pulse waves tended to be as large when ventricular systole coincided with the early part of the period of inflow resulting from auricular systole. At such a time one might expect greater change in ventricular initial tension than filling.[15] The gradual decline in amplitude of pulse waves as ventricular beats fell later and later in the period of auricular diastole, however, could scarcely be attributed to changes in initial tension. This decline is probably related mainly to differences in degree of ventricular filling.[16]

It will be noted that while the size of the pulse waves bears a definite relationship to the P-R measurement, other minor variations are present. For these lesser variations there are at least three possible causes: (1) defects in technic of recording (movements of wrist, etc.), (2) respiratory variations and (3) completeness of ventricular emptying in the preceding beat.[17]

Variations in Sound Intensity.—With the exception of relatively minor discrepancies, the variations of intensity of the first sound in all seven cases studied bore an unmistakable relation to the length of the P-R intervals. In five of the seven cases (all except those of the woman with mitral and aortic valvular defects and the boy in whom no short

14. This view is based on the time incidence of the murmurs in this and other cases and the fact that they are loudest in early ventricular diastole when the greatest blood flow from auricles to ventricles is possible.

15. Wiggers, C. J.: The Pressure Pulses in the Cardiovascular System, New York, Longmans Green & Company, 1928, p. 55.

16. Wiggers (The Circulation in Health and Disease, Philadelphia, Lea & Febiger, 1923, p. 96) stated that if the As-Vs interval is sufficiently long, volume curves show a back flow from ventricles to auricles. Ventricular filling might therefore be expected to reach a peak at the end of the period of blood flow caused by auricular systole and then temporarily decline.

17. There was slight auricular arrhythmia in case 1 so that constant or predictable A-V relationships were not maintained. Thus the beats having a certain time relation might be preceded by beats with varying intervals and consequently varying emptying.

P-R intervals were recorded) there was remarkable similarity in the reduction of sound intensity toward the long side of the normal P-R range. The decline to faint sounds was in some cases completed within the normal P-R range, but in others was delayed until the P-R interval was as long as 0.24 second.

In these five cases the sounds were of maximum intensity when the P-R intervals were very short. In cases 1, 2, 3 and 6, it was possible to study the time relationships of the increase in sounds. In all of these cases moderately increased intensity occurred even when ventricular electric systole preceded the auricular systole by a few hundredths of a second. When auricular systole slightly preceded ventricular, and in one case in which the two were simultaneous, maximum sounds occurred. These relationships are shown in figure 2.

With markedly prolonged P-R intervals two distinct types of sound variation were noted. In the two young patients (cases 4 and 5), when the P-R interval reached 0.34 and 0.32 second, respectively, the sounds began to become louder. Of the three older patients in whom observations could be made during this range, none showed the late increase of sound intensity.

The differences in relationship of the changes of sound intensity to the duration of the P-R intervals in the patient with valvular disease (case 7, mitral stenosis and aortic regurgitation) were striking. Instead of loud first sounds in association with very short P-R intervals, as the other cases showed, they were relatively faint. As the P-R intervals lengthened toward the upper range of normal, the sounds increased. Thus the relationship seemed to be just the reverse of those recorded in the nonvalvular cases.

Factors Concerned in Variations of the First Sound.—Griffith's [2] suggestion that for the production of the loud sounds it may be necessary for the auricle to be in systole at the time the ventricle enters into contraction is shown by figure 2 to be inadequate. Nevertheless, he deserves full credit for making this observation with the methods of study available. We have thus far not observed the reduplication of the first sound mentioned by Lewis [3] when ventricular slightly precedes auricular contraction, although we have recorded it when the reverse relation is present.

We have discussed our reasons for accepting the view that the differences in amplitude of pulse waves recorded are due largely to such dynamic factors as the degree of ventricular filling and initial tension. It is obvious from the time relationships of the changes of intensity of sounds that such factors must assume at most a minor rôle in causing the inequalities of sound. Consequently, Read's [6] recent suggestion that the inequalities of sound are associated with varying ventricular outputs receives no support from our work.

It may be assumed as a provisional hypothesis that the inequalities of sound depend on the position of the mitral leaflets at the beginning of ventricular contraction. The data available do not warrant an attempt to elaborate this hypothesis, but there are certain facts in support of it deserving mention.

Wiggers [18] stated that the sound intensity varies directly as the systolic tension developed within the ventricles, and there is good reason to believe that it is with the tension developed during the isometric period of systole.

This statement at once suggests the possible importance of the position of the mitral leaflets at the beginning of ventricular systole in modifying the first sound. If the leaflets happened to be widely open, at least slight regurgitation might occur, thus retarding the development of intraventricular tension.[19] If, however, the leaflets happened to be near a position of closure at the beginning of ventricular systole, little or no regurgitation might be expected to take place, thus permitting a more rapid rise of intraventricular tension and consequently a louder first sound.

It is a well known clinical fact that the presence of mitral insufficiency tends to weaken the first sound and frequently obliterates it entirely. On the other hand, mitral stenosis with its relatively rigid mitral leaflets is usually accompanied by a sharp loud first sound. If, however, regurgitation is associated with stenosis the sharpness of the first sound tends to be lessened and with marked regurgitation may be completely obliterated.

There is direct evidence to the effect that the position of the mitral leaflets is altered by auricular systole. Dean's [20] curves of movements of the leaflets appear to show that shortly after the beginning of auricular systole they tend toward a position of closure (up to 0.147 second) but quickly open. These experiments were done on perfused cats' hearts; consequently, one might venture the assumption that in human beings with larger hearts and consequently larger leaflets, the period in some cases might be prolonged a few hundredths of a second. If such an assumption is justified, the curves of decreasing intensity

18. Wiggers, C. J.: The Circulation in Health and Disease, Philadelphia, Lea & Febiger, 1923, p. 324.

19. One would expect very little regurgitation of blood, but there might be no inconsiderable regurgitation of pressure. The experiments of C. J. Wiggers and H. S. Feil (The Cardiodynamics of Mitral Insufficiency, Heart **9**:149 [April] 1922) show surprisingly little alteration in the dynamics of ventricular contraction in the presence of mitral regurgitation. It seems possible, however, that slight changes in the development of intraventricular tension might have an important influence on the first heart sound.

20. Dean, A. L., Jr.: Movements of the Mitral Cusps in the Cardiac Cycle, Am. J. Physiol. **40**:206 (April) 1916.

of sound, which occur within the normal range of P-R intervals and slightly beyond it, could be definitely related to movements of the mitral leaflets from a position near the closure to the opening. It will be noted that in each instance the transition period (sounds of intermediate intensity) is extremely brief.

On the basis of what knowledge we have regarding the dynamic factors concerned in contraction, we are unable to account for the fact that in three of our cases (cases 1, 2 and 3) the first sounds remain relatively weak when the P-R intervals are long, whereas in two cases (cases 4 and 5) they assume the maximum intensity. It occurred to us that possibly the variable factors in these two groups of cases might also be the position of the mitral leaflets.

The two patients who had maximum sound intensity with long P-R intervals were both children with presumably thin, pliable leaflets which might more readily float back toward a position of closure during the period of relative inactivity than the leaflets of the older patients. We have no evidence for this assumption, but no other reasonable explanation for these variations in sound presents itself.

A moderate increase of sound intensity occurred regularly in four cases (cases 1, 2, 3 and 6) when ventricular electric systole preceded auricular systole by a few hundredths of a second. Obviously, these changes in sound must be the result of auricular contraction, but it does not seem reasonable to suppose that either change in position of leaflets or any change in the ventricular status could have been brought about by auricular systoles with this time relationship. It seemed to us, therefore, that there might be significance in the fact that as ventricular pressure was rising as a result of contraction, auricular pressure was also beginning to rise. These conditions could be expected to minimize regurgitation of pressure from the ventricles and thus favor a more rapid rise of intraventricular tension (and therefore a louder sound).

It is fairly generally accepted, although not clearly established, that closure of the A-V valves furnishes a component of the normal first heart sound. It is necessary, therefore, to consider what part valve closure might play in the variations that have been described. No direct evidence can be furnished on this point. It would seem certain, however, that valve closures cannot contribute to the increase of the first sound, which was repeatedly observed when ventricular systole slightly preceded auricular. Furthermore, if variations in the valvular element of the first sound were important one would expect the loudest sounds when the beginning of ventricular systole found the leaflets widely open (permitting momentum to be acquired during closure) and the faintest sounds when the leaflets were already near a position of closure. If the results of Dean's [20] experiments on the time incidence of valve movements may be applied to the human heart, the ventricular

beats associated with loud sounds and short P-R intervals would begin with the leaflets near the position of closure. Faint sounds occurred in case 1 when the evidence indicated that the blood was flowing rapidly from the auricles to the ventricles, so that the leaflets could not have been near closure.

The changes in intensity of sound in our patient with mitral stenosis and aortic regurgitation were of particular interest in that the time relationships of change were so different from those of all other cases. A sound tracing recently published by Schellong [21] made from a patient with mitral stenosis and incomplete heart block showed inequalities of the first sound. The P-R intervals of the accompanying electrocardiogram were all longer than those observed in our patient with mitral stenosis, so that the two cannot be compared directly, although the data in the two cases are in a sense complementary. The curves can be compared with those of our case 5 in which there was no evidence of mitral stenosis, but incomplete block with the P-R intervals of similar duration was present. In Schellong's case the intensity of the first sound was greatest when the P-R interval was only slightly prolonged (0.23 second), but with longer intervals the intensity was reduced. This is just the opposite relation to that observed in our case 5, thus suggesting that mitral stenosis was responsible for the difference. If the observations in Schellong's case are added to those of our subject with mitral stenosis (case 7, fig. 2) a curve is obtained suggesting that mitral stenosis causes a delay in the curve of rise and fall of intensity of the first sound with reference to the duration of the P-R intervals. Further observations on patients with mitral stenosis and shifting As-Vs relations will be necessary to establish this point.

Clinical Significance of Inequalities of the First Sound.—We have mentioned that the inequalities of sound may be utilized as an auscultatory sign of dissociated beating (heart block or ventricular escape.[22]). Their recognition on auscultation depends solely on whether one remembers to compare the intensity from beat to beat. When the clinical test is made, it is advisable to have the patient hold his breath for periods long enough to exclude variations due to respiration.

The fact that marked inequalities of sound may occur within the normal range of auriculoventricular relations (fig. 2) would appear to have wide clinical significance. There is a tendency among clinicians, perhaps not without justification, to attach importance to the characteristics of the first sound as evidence of the vigor of ventricular

21. Schellong, F.: Mitral Stenosis Murmur in Conduction Disturbance, Klin. Wchnschr. **8**:2042 (Oct. 29) 1929.

22. The inequalities of the first sound, which occur in extrasystolic and auricular fibrillation, are easily differentiated. In these conditions the variations are noted in connection with ventricular irregularity.

contraction. The penetrating researches of Wiggers [18] in this field have lent some support to this view. It is generally appreciated that such factors as the thickness of the wall of the chest and the presence or absence of valvular defects must be discounted before significance is attached to the intensity or the quality of the sound.

We wish to offer the suggestion that the duration of the auriculoventricular interval within the normal range may have importance in determining the character of the sound. This suggestion is strongly supported by the evidence we have obtained in our cases of dissociated beating. Thus it is probable that the loud first sounds so frequently heard when the P-R intervals are short (approximately from 0.12 to 0.15 second) owe part of their intensity, at least in some cases, to the proximity of the auricular and ventricular contraction. It is equally probable that in certain cases with longer P-R intervals (approximately from 0.18 to 0.21 second) the relatively weak first sound is affected by the length of the period between auricular and ventricular contractions.[23]

We do not wish to stress unduly the importance of the auriculoventricular interval in determining the character of the first heart sound. It is only one of a number of factors involved, and under certain circumstances not well understood may vary or be entirely negligible (as was shown in case 1). Nevertheless, it is a factor that should be reckoned with, and failure to do so may vitiate clinical deductions based on the character of the first sound.

SUMMARY

1. A series of seven cases with varying auriculoventricular relationships all showed inequalities of the first heart sound which could be related to the lengths of the intervals between auricular and ventricular systoles. These time relations tended to be characteristic for each case, although the degree of inequality varied and exceptionally could not be recorded.

2. The inequalities of sound are easily detected by auscultation and furnish a valuable clinical test of dissociated beating of the auricles and ventricles (complete heart block and ventricular escape). The absence of inequality of sound does not rule out the possibility of dissociated beating.

3. In two cases (both having complete heart block) inequalities in the size of the pulse waves were recorded. When the amplitude of the waves recorded was compared with the lengths of intervals between auricular and ventricular systoles, a definite relation was revealed. In

23. The evidence obtained in a study of the inequalities of the first sound of extrasystoles (to be reported) also points to the importance of As-Vs relations as a factor governing the intensity of the sound.

both cases the curves showed similar time relations. In one, inequalities in amplitude seemed to vary from day to day, and occasionally no differences could be recorded. In three other cases tracings of the pulse waves failed to reveal changes in the amplitude of the waves that could be related to the auriculoventricular intervals.

4. Simultaneous records of changes in the intensity of sound and amplitude of the pulse waves showed that either comparatively loud or faint sounds may be associated with comparatively large or small pulse waves. It was therefore concluded that while both types of changes were dependent on phenomena resulting from auricular systole, the factors concerned were not identical.

5. It is suggested, principally on the basis of work by Wiggers and by Gesell and some indirect evidence obtained by us, that the changes observed in the amplitude of the pulse waves are due principally to the effects of auricular systole on ventricular filling and initial tension.

6. The provisional hypothesis is adopted that inequalities of the first heart sound observed are due principally to variation in the position of the mitral leaflets at the beginning of ventricular contraction.

7. The data presented indicate that in the clinical evaluation of the first heart sound as evidence of cardiac vigor, modifications dependent on the duration of the auriculoventricular interval should be discounted.

Prof. Charles Weyl of the Moore School of Electrical Engineering of the University of Pennsylvania constructed the three stage transformer coupled amplifier.

Book Reviews

TREATMENT IN GENERAL PRACTICE. By HARRY BECKMAN, M.D., Professor of Pharmacology and Therapeutics, Marquette University Medical School. Price, $10. Pp. 899. Philadelphia: W. B. Saunders Company, 1930.

This book is a comprehensive treatise of therapy written by a teacher of pharmacology and therapeutics for the student and general practitioner of medicine. The author feels that, with few notable exceptions, the teaching of therapeutics is more or less neglected, usually consisting of a formal course of lectures to junior students, supplemented later by what little instruction may be given to senior students during hours in the clinic in the various departments. The latter is usually rather sketchy "simply because in the (teacher's) immersion in the task of acquainting the student with the prodigious methodology of modern diagnosis, no time is left for an exhaustive consideration of the treatment of disease."

The book has been carefully edited, is printed in clear type on good paper and is arranged by systems, i. e., infectious and parasitic diseases, constitutional diseases such as allergy, deficiency diseases and metabolic disorders, diseases of the gastro-intestinal tract, the respiratory, excretory, circulatory and nervous systems and the integument, followed by a consideration of drug addiction, poisons, burns, obstetrics and miscellany.

To quote from the preface, "Therapy has been evolved out of the experience of physicians all over the world. The true authors of the book, then, are those men and women whose names appear in the Bibliography. Whenever possible, I have presented their work in their own words, but often it has been necessary to abstract and condense. . . ." Each disease condition is defined, and there is a brief statement of the etiology, symptomatology and usual course, followed by a thorough discussion of therapy and prophylaxis. There are numerous prescriptions and tables, an extensive bibliography and an index. This treatise should prove a valuable aid to the student and practitioner.

INDEX TO VOLUME 46

Book Reviews are grouped together and are indexed under that heading in alphabetical order, under the letter B.

PAGE

Addison's Disease, geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris..... 741

in a Negro, report of a case..... 375

Adkinson, J.: Frequent chest colds, variability in their occurrence and bacteriology of those very susceptible to this type of cold..... 1

Allergy: See Anaphylaxis and Allergy

Althausen, T. L.: Modification of dextrose tolerance test as an index of metabolic activity of liver..... 482

Alvarez, W. C.: Blood pressure in 6000 prisoners and 400 prison guards..... 17

digestion; efficiency with various foods and under various conditions..... 361

Amyloidosis, relation of lipoid nephrosis to 137

Anaphylaxis and allergy; diffusible calcium of blood serum in allergic diseases.... 72

fatal human anaphylactic shock with autopsy findings and review of literature 306

Andersch, M.: Metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight....1002

Anderson, S. V.: Erythrocyte sedimentation test in tuberculosis, study of 2000 cases 787

Anemia, iron metabolism in pernicious and in secondary anemia..... 458

pernicious, blood regeneration during early remission 417

pernicious, geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris..... 741

pernicious, neutral red test in..... 979

red blood cell size in anemia; its value in differential diagnosis..... 440

Angina pectoris, geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris..... 741

Appendix, reflex influence of colon, appendix, and gallbladder on stomach..... 988

Artery, coronary, appearance time of T wave changes in electrocardiogram following acute coronary occlusion, reports of 2 cases 657

Arthritis, chronic; bacteriology of affected tissues 121

Asthma, bronchial, severe chronic intractable type..... 218

Bannick, E. G.: Action and excretion of nitrates 797

Banyl, A. L.: Erythrocyte sedimentation test in tuberculosis, study of 2,000 cases 787

Bargen, J. A.: Serum treatment for chronic ulcerative colitis.....1039

PAGE

Baumgartner, E. A.: Tropical sprue; experience with 36 cases..... 597

Beard, M.: Diabetes mellitus; colloidal osmotic pressure of blood..... 752

Bile salts, specific effect of bile salts on pneumococci and on pneumococcus pneumonia 644

Black, I.: Postoperative results in toxic goiter 266

Blood: See also Erythrocytes; Leukocytes chemistry, postmortem, in renal disease.. 283

colloidal osmotic pressure of blood and diabetes mellitus..... 752

diffusible calcium and proteins of blood serum in malignant disease..... 67

diffusible calcium of blood serum in allergic diseases..... 72

nonprotein nitrogenous constituents in... 290

oxygen and carbon dioxide content of blood from internal jugular and other veins 630

plasma proteins..... 236

platelets, an improved indirect method for their enumeration..... 585

pressure, high, differentiation and diagnosis of certain ophthalmoscopic pictures in hypertensive disease..... 901

pressure, high, evaluation of prognosis.. 227

pressure, high; so-called malignant hypertension, clinical and morphologic study 75

pressure in 6000 prisoners and 400 prison guards 17

sugar, arteriovenous difference in blood sugar content..... 605

sugar, diagnostic value of sugar tolerance curve in endocrinopathies..... 984

sugar; intermediate metabolism of foreign sugars 321

transfusion from a group II (a) donor to a group III (b) recipient without fatal result 502

Bolkan, W. S.: Gastric sequelae of corrosive poisoning..... 342

Boltz test in urinalysis..... 778

Bone changes and parathyroid tumor..... 506

Book Reviews:

Basis of epilepsy; E. Tracy..... 900

Baby's First Two Years; B. M. Smith... 360

Chest, (The); L. R. Sante..... 552

Clinical Examination of Nervous System; G. H. Monrod-Krohn..... 900

Diagnostische und Therapeutische Irrtümer und deren Verhütung—Innere Medizin; Erstes Heft, Krankheiten des Stoffwechsels; S. Isaac..... 360

Die Arten der Schlaganfalle des Gehirns und Ihre Entstehung; P. Schwartz..... 900

Edema and Its Treatment; H. Elwyn..... 162

Essentials of Medical Diagnosis; T. Horder and A. E. Gow..... 163

Handbuch der Ernährungslehre, Band II: Spezielle Diatetik der Krankheiten des Verdauungsapparates. Teil 1:Magen; C. von Noorden..... 360

PAGE

BOOK REVIEWS—Continued

Hipertension Arterial: Hipertonia arterial o hiperpiesis y los estados hypertensivos hipertonicos o de hiperpiesia; M. R. Castex 161

Hypertension and Nephritis; A. B. Fishberg 358

Praktische Differentialdiagnostik für Aerzte und Studierende. Herausgegeben von G. Honigmann. Band III. Differentialdiagnostik in der Psychiatrie; H. Haymann 552

Sindrome de Oclusion Coronaria; Battro.. 899

Some Aspects of the Cancer Problem; W. B. Bell 898

Symptoms of Visceral Disease. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine; F. M. Pottenger..... 899

Three Minute Medicine. A Series of Brief Essays on Popular Medicine; L. R. Effler 164

Treatment in General Practice; H. Beckman 1072

Urticaires; E. Joltrain..... 900

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung: II. Tagung. Herausgegeben von Prof. Dr. Bruno Kisch 164

Brice, A. T., Jr.: Boltz test in urinalysis.. 778

Brown, G. E.: Peripheral arterial disease in polycythemia vera..... 705

Bullowa, J. G. M.: Fatal human anaphylactic shock; report of case with autopsy findings and review of literature..... 306

Burnham, L.: Transfusion from a group II (a) donor to a group III (b) recipient without fatal result..... 502

Byrd, H.: Sphenopalatine phenomena; present status of knowledge.....1026

Byrd, W.: Sphenopalatine phenomena; present status of knowledge.....1026

Calcium, diffusible calcium and proteins of blood serum in malignant disease..... 67

diffusible calcium of blood serum in allergic diseases..... 72

Cancer, carcinomatous degeneration of polyp of stomach; report of 3 personal cases with review of 24 recorded by others.. 841

diffusible calcium and proteins of blood serum in malignant disease..... 67

primary carcinoma of lungs with metastases to central nervous system..... 680

primary, of liver..... 105

Cardiovascular disease; differentiation and diagnosis of certain ophthalmoscopic pictures in hypertensive diseases..... 901

Childrey, J. H.: Digestion: efficiency with various foods and under various conditions 361

Chung, H. L.: Antibody formation in kalazar 782

Clarke, N. E.: Postoperative results in toxic goiter..... 266

Climate, does climate affect human conception rate? 921

geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris 741

Cohen, S. J.: Neutral red test in pernicious anemia 979

PAGE

Colds, frequent chest colds: variability in their occurrence and bacteriology in those very susceptible to this type of cold 1

Colitis, serum treatment for chronic ulcerative colitis.....1039

Colon, reflex influence of colon, appendix and gallbladder on stomach..... 988

Conception, does climate affect human conception rate?..... 921

Connery, J. E.: Correlation of Widal's postdigestive leukopenia as test for liver function with normal rhythm of leukocytes 1018

Corrosive Poisoning: See Mercuric chloride

Daland, G. A.: Life of reticulocytes; experiments on their maturation..... 553

Metabolism of normal and leukemic leukocytes 46

Dalton, J. B.: Diffusibe calcium and proteins of blood serum in malignant disease 67

Dameshek, W.: Acute monocytic (histiocytic) leukemia, review of literature and case reports..... 718

Davison, C.: Primary carcinoma of lungs with metastases to central nervous system 680

Dextrose, modification of dextrose tolerance test as index of metabolic activity of liver 482

Diabetes Mellitus, colloidal osmotic pressure of blood in..... 752

is climate a responsible factor in etiology? 569

sugar consumption in its etiology..... 582

Digestion; efficiency with various foods and under various conditions..... 361

Diphtheria, hazard of incision for apparent quinsy in diphtheria..... 402

Dolin, B. T.: Intermediate metabolism of foreign sugars..... 321

Dorsey, A. H. E.: Chronic arthritis; bacteriology of affected tissues..... 121

Duodenal Ulcer: See Peptic ulcer

Dwyer, H. V.: Peripheral neuritis complicated by massive collapse of lung following tonsillectomy..... 833

Electrocardiogram: See under Heart

Eliason, E. I.: Carcinomatous degeneration of polyp of stomach: report of 8 personal cases with review of 24 recorded by others..... 841

Endocrine glands, diagnostic value of sugar tolerance curve in endocrinopathies... 984

Enema, evaluation of expulsion of enemas as a criterion of intestinal obstruction.. 669

Epigastric pulsation; classification in regard to form of epigastriogram..... 333

Epilepsy, laboratory studies in..... 180

Erythrocyte sedimentation test in tuberculosis, study of 2,000 cases..... 787

red blood cell size in anemia; its value in differential diagnosis..... 440

Exercise, after-effect of muscular exercise on production of basal heat; metabolism of obesity..... 40

PAGE

Fasting, G. F. C.: Serum treatment for chronic ulcerative colitis.....1039

Fauley, G. B.: Experimental gastric ulcer; effect of consistency of diet on healing 524

Felsen, J.: Laboratory studies in epilepsy.. 180

Fishberg, A. M.: Differentiation and significance of certain ophthalmoscopic pictures in hypertensive diseases..... 901

Fishberg, E. H.: Intermediate metabolism of foreign sugars..... 321

Fitzhugh, G.: Red blood cell size in anemia, its value in differential diagnosis..... 440

Frisch, I. A.: Demonstration of local immunity of peritoneum by means of Shwartzman phenomenon..... 410

Fukui, N.: Epigastric pulsation; classification in regard to form of epigastriogram 333

Gallbladder, reflex influence of colon, appendix and gallbladder on stomach..... 988

Gastric Ulcer: See Peptic ulcer

Giffin, H. Z.: Peripheral arterial disease in polycythemia vera..... 705

Glassberg, B. Y.: Arteriovenous difference in blood sugar content..... 605

Diagnostic value of sugar tolerance curve in endocrinopathies..... 984

Glover, E. C.: Metabolism of normal and leukemic leukocytes..... 46

Goehl, R. O.: Evaluation of expulsion of enemas as criterion of intestinal obstruction 669

Goiter, exophthalmic; geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris.. 741

exophthalmic, nature of Graves' disease 610

exophthalmic, thyrotoxicosis following subtotal thyroidectomy for..... 946

toxic, postoperative results..... 266

Goodman, M.: Correlation of Widal's postdigestive leukopenia as test for liver function with normal rhythm of leukocytes 1018

Gordon, J. E.: Hazard of incision for apparent quinsy in diphtheria..... 402

Graves' Disease: See Goiter, exophthalmic

Gray, I.: Neutral red test in pernicious anemia 979

Greenberg, D. M.: Diffusible calcium and proteins of blood serum in malignant disease 67

Diffusible calcium of blood serum in allergic diseases..... 72

Grill, J.: So-called malignant hypertension; clinical and morphologic study..... 75

Gunther, L.: Diffusible calcium and proteins of blood serum in malignant disease 67

Diffusible calcium of blood serum in allergic diseases..... 72

Modification of dextrose tolerance test as an index of metabolic activity of liver 482

Hawks, J. E.: Influence of special breakfast on basal metabolism of patients with pathologic condition..... 316

PAGE

Heart, appearance time of T wave changes in electrocardiogram following acute coronary occlusion; report of 2 cases.. 657

influence of auricular contraction on first heart sound and radial pulse.....1048

resuscitation of stopped heart by intracardiac therapy..... 553

significance of electrocardiogram with large Q in lead 3..... 470

Heath, C. W.: The life of reticulocytes; experiments on their maturation..... 533

Hershey, E.: Postmortem blood chemistry in renal disease 283

Horwitz, W. A.: Primary carcinoma of lungs with metastases to central nervous system 680

Hubbard, R. S.: Alkaline tide as method of studying gastric acidity..... 994

Hurxthal, L. M.: Appearance time of T wave changes in electrocardiogram following acute coronary occlusion, report of 2 cases..... 657

Hyman, A. S.: Resuscitation of stopped heart by intracardiac therapy..... 553

Hyperglycemia: See Blood, sugar

Hypertension, Arterial: See Blood pressure, high

Immunity, demonstration of local immunity of peritoneum by means of Shwartzman phenomenon..... 410

Injection, intracardiac, resuscitation of stopped heart by intracardiac therapy 553

Intestine, obstruction; evaluation of expulsion of enemas as a criterion of intestinal obstruction..... 669

Iron metabolism in pernicious and in secondary anemia..... 458

Ivy, A. C.: Experimental gastric ulcer; effect of consistency of diet on healing..... 524

Jacobi, M.: Addison's disease in a Negro, report of a case..... 375

Fatal human anaphylactic shock, report of case with autopsy findings and review of literature..... 306

Jewett, C. H.: Tropical sprue; experience with 36 cases..... 597

Kahn, I. S.: Bronchial asthma, severe chronic intractable type..... 218

Kala-Azar: See Leishmaniasis

Kartoon, L. B.: Effects of intravenous injections of foreign protein on peptic ulcer 768

Keith, N. M.: Action and excretion of nitrates 797

Kerr, W. J.: Modification of dextrose tolerance test as index of metabolic activity of liver..... 482

Kidney disease, postmortem blood chemistry in..... 283

lipoid nephrosis, pathology, genesis and relation to amyloidosis..... 137

ophthalmoscopic pictures in hypertensive diseases 901

Lagen, J. B.: Modification of dextrose tolerance test as index of metabolic activity of liver..... 482

PAGE

Lederer, M.: Postmortem blood chemistry in renal disease..... 283

Leishmaniasis, antibody formation in kala-azar 782

Lennox, W. G.: Oxygen and carbon dioxide content of blood from internal jugular and other veins..... 630

Leukemia, acute monocytic (histiocytic) leukemia, review of literature and case reports 718

Leukocytes, metabolism of normal and leukemic leukocytes..... 46

Leukopenia, correlation of Widal's post-digestive leukopenia as test for liver function with normal rhythm of leukocytes 1018

Lipoid nephrosis, pathology, genesis and relation to amyloidosis..... 137

Liver, carcinoma of, primary..... 105

function, correlation of Widal's post-digestive leukopenia as test for liver function with normal rhythm of leukocytes 1018

modification of dextrose tolerance test as index of metabolic activity of liver.... 482

Lung, peripheral neuritis complicated by massive collapse of lung following tonsillectomy 833

primary carcinoma of lungs with metastases to central nervous system..... 680

Mann, F. C.: Digestion: efficiency with various foods and under various conditions 361

Margolies, A.: Influence of auricular contraction on first heart sound and radial pulse 1048

Margolis, H. M.: Chronic arthritis: bacteriology of affected tissues..... 121

Matzner, M. J.: Neutral red test in pernicious anemia..... 979

Meckel's Ganglion: See Sphenopalatine ganglion

Merbaphen, renal damage following administration of merbaphen (novasurol).494

Mercuric chloride poisoning, gastric sequelae of..... 342

Metabolism, basal: influence of special breakfast on basal metabolism of patients with pathologic condition..... 316

in experimental yellow fever..... 290

intermediate of foreign sugars..... 321

low basal metabolism without myxedema.. 879

of normal and leukemic leukocytes..... 46

of obesity; after-effect of muscular exercise on production of basal heat..... 40

of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....1002

Meyer, J.: Effects of intravenous injections of foreign protein on peptic ulcer..... 768

Miller, G. H.: Reflex influence of colon, appendix and gallbladder on stomach.. 988

Miller, T. G.: Carcinomatous degeneration of polyp of stomach; report of 8 personal cases with a review of 24 recorded by others..... 841

PAGE

Mills, C. A.: Diabetes mellitus. Is climate a responsible factor in etiology?..... 569

Diabetes mellitus, sugar consumption in its etiology..... 582

Does climate affect human conception rate? 921

Geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris..... 741

Morrell, C. A.: Chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys 382

Chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys; concentration of nonprotein nitrogenous constituents in blood..... 290

Morris, A. E.: Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter 946

Moschcowitz, E.: Nature of Graves' disease 610

Murphy, F. D.: So-called malignant hypertension; clinical and morphologic study 75

Murphy, W. P.: Red blood cell size and anemia; its value in differential diagnosis 440

Myxedema, low basal metabolism without.. 879

Negro, Addison's disease in a Negro, report of case..... 375

Nephrosis: See under Kidney

Neuritis, peripheral neuritis complicated by massive collapse of lung following tonsillectomy 833

Nitrates, action and excretion of..... 797

Novasurol: See Merbaphen

Obesity, metabolism of obesity; after-effect of muscular exercise on production of basal heat..... 40

metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....1002

Olef, I.: Blood platelets; improved indirect method for their enumeration..... 585

Ophthalmoscopic pictures in hypertensive diseases 901

Oppenheimer, B. S.: Differentiation and significance of certain ophthalmoscopic pictures in hypertensive diseases..... 901

Palmer, W. L.: Value of acid neutralization in treatment of gastric and duodenal ulcers 165

Parathyroid tumor and changes of bones... 506

Pardee, H. E. B.: Significance of electrocardiogram with a large Q in lead 3.... 470

Peptic ulcer, effects of intravenous injections of foreign protein on peptic ulcer. 768

experimental gastric ulcer; effect of consistency of diet on healing..... 524

value of acid neutralization in treatment of gastric and duodenal ulcers..... 165

Peritoneum, demonstration of local immunity of peritoneum by means of Shwartzman phenomenon..... 410

Perspiration: See Sweat and sweat glands

Pitts, H. H.: Primary carcinoma of liver.. 105

PAGE

Pneumococci and pneumococcus pneumonia, specific effect of bile salts on..... 644

Pneumonia, specific effect of bile salts on pneumococci and on pneumococcus pneumonia 644

Polayes, S. H.: Postmortem blood chemistry in renal disease..... 283

Polycythemia vera, peripheral arterial disease in..... 705

Polyp, carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others... 841

Proteins, diffusible calcium and proteins of blood serum in malignant disease..... 67
effects of intravenous injections of foreign protein on peptic ulcer..... 768
plasma 236

Pulsation, epigastric: classification in regard to form of epigastriogram..... 333

Quinsy: See Tonsillitis

Rabinowitch, I. M.: Diabetes mellitus; colloidal osmotic pressure of blood..... 752
Origin of urobilinogen; a clinical experiment 1014

Reimann, H. A.: Antibody formation in kala-azar 782

Respiratory tract: frequent chest colds; variability in their occurrence and bacteriology in those very susceptible to this type of cold..... 1

Reticulocytes; life of reticulocytes; experiments on their maturation..... 533

Retina in hypertensive diseases..... 901

Riddle, M. C.: Pernicious anemia; blood-regeneration during early remission.... 417

Riecker, H. H.: Iron metabolism in pernicious and in secondary anemia..... 458

Rosenow, E. C.: Serum treatment for chronic ulcerative colitis.....1039

Sala, A. M.: Addison's disease in Negro, report of a case..... 375

Schmitz, H. L.: Metabolism of normal and leukemic leukocytes..... 46

Senior, F. A. (Mrs.): Does climate affect human conception rate?..... 921

Shapiro, P. F.: Lipoid nephrosis; pathology, genesis and relation to amyloidosis 137

Shwartzman phenomenon, demonstration of local immunity of peritoneum by means of 410

Singer, H. A.: Gastric sequelae of corrosive poisoning 342

Smith, E.: Metabolism of obesity; after-effect of muscular exercise on production of basal diet..... 40

Smith, F. M.: Reflex influence of colon, appendix and gallbladder on stomach..... 988

Snapper, I.: Parathyroid tumor and changes of bones 506

Sphenopalatine phenomena; present status of knowledge 1026

Sprue, tropical sprue, experience with 36 cases 597

PAGE

Sprunt, D. H.: Renal damage following administration of merbaphen (novasurol) 494

Stanley, L. L.: Blood pressure in 6,000 prisoners and 400 prison guards..... 17

Stieglitz, E. J.: Arterial hypertension, evaluation of prognosis..... 227

Stomach acidity, alkaline tide as method of studying gastric acidity..... 994
carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others..... 841
experimental gastric ulcer; effect of consistency of diet on healing..... 524
function, neutral red test in pernicious anemia 979
reflex influence of colon, appendix and gallbladder on stomach..... 988
Ulcer: See Peptic ulcer

Strong, G. F.: Primary carcinoma of liver.. 105

Strouse, S.: Metabolism of obesity: after-effect of muscular exercise on production of basal heat..... 40
Metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....1002

Sugars, foreign, intermediate metabolism of. 321

Sweat and sweat glands: metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....1002

Thompson, P. K.: Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter..... 946

Thompson, W. O.: Low basal metabolism without myxedema..... 879
Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter..... 946

Thrush: See Sprue

Thurmon, F. M.: Low basal metabolism without myxedema..... 879

Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter..... 946

Tonsillectomy, peripheral neuritis complicated by massive collapse of lung following tonsillectomy..... 833

Tonsillitis, hazard of incision for apparent quinsy in diphtheria..... 402

Tuberculosis, erythrocyte sedimentation test in, study of 2,000 cases..... 787
pulmonary, treatment in allergen-proof chambers 637

Tumor, parathyroid tumor and changes of bones 506

Turner, A. H.: Vital capacity in college women: standards for normal vital capacity in college women..... 930
Vital capacity in college women; study of students with high and low vital capacity 938

Ulcer, Gastric: See Peptic Ulcer

Urine, alkaline tide as method of studying gastric acidity..... 994
Boltz test in urinalysis..... 778

Urobilinogen, origin of; a clinical experiment 1014

PAGE

van Leeuwen, W. S.: Pulmonary tuberculosis; treatment in allergen-proof chambers 637

Vital Capacity in college women; standards for normal vital capacity in college women 930

in college women; study of students with high and low vital capacity..... 938

Wakeman, A. M.: Chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys..... 382

Chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys; concentration of nonprotein nitrogenous constituents in blood..... 290

Walker, I. C.: Frequent chest colds, variability of their occurrence and bacteriology in those very susceptible to this type of cold..... 1

Wang, C. C.: Influence of special breakfast on basal metabolism of patients with pathologic condition..... 316

Metabolism of obesity; after-effect of muscular exercise on production of basal heat 40

Metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....1002

PAGE

Wangensteen, O. H.: Evaluation of expulsion of enemas as a criterion of intestinal obstruction..... 669

Whelan, M.: Action and excretion of nitrates 797

Wiener, H. J.: Plasma proteins..... 236

Wiener, R. E.: Plasma proteins..... 236

Wolferth, C. C.: Influence of auricular contraction on first heart sound and radial pulse 1048

Wright, V. W. M.: Carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others..... 841

Yellow fever, chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys..... 382

chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys; concentration of nonprotein nitrogenous constituents of blood..... 290

Young, D. C.: Hazard of incision for apparent quinsy in diphtheria..... 402

Ziegler, E. E.: Specific effect of bile salts on pneumococci and on pneumococcus pneumonia 644

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CONTENTS

PAGE

THE DIFFERENTIATION AND SIGNIFICANCE OF CERTAIN OPHTHALMOSCOPIC PICTURES IN HYPERTENSIVE DISEASES. ARTHUR M. FISHBERG, M.D., AND B. S. OPPENHEIMER, M.D., NEW YORK 901

DOES CLIMATE AFFECT THE HUMAN CONCEPTION RATE? C. A. MILLS, M.D., AND MRS. F. A. SENIOR, CINCINNATI 921

VITAL CAPACITY IN COLLEGE WOMEN. ABBY H. TURNER, PH.D., SOUTH HADLEY, MASS.:
I. STANDARDS FOR NORMAL VITAL CAPACITY IN COLLEGE WOMEN .. 930
II. A STUDY OF STUDENTS WITH HIGH AND LOW VITAL CAPACITY 938

THYROTOXICOSIS FOLLOWING SUBTOTAL THYROIDECTOMY FOR EXOPHTHALMIC GOITER. WILLARD OWEN THOMPSON, M.D., CHICAGO; ALBERT E. MORRIS, M.D., BOSTON, AND PHEBE K. THOMPSON, M.D., CHICAGO 946

THE NEUTRAL RED TEST IN PERNICIOUS ANEMIA. S. J. COHEN, M.D.; M. J. MATZNER, CH.E., M.D., AND IRVING GRAY, M.D., BROOKLYN ... 979

THE DIAGNOSTIC VALUE OF THE SUGAR TOLERANCE CURVE IN ENDOCRINOPATHIES. B. Y. GLASSBERG, M.D., ST. LOUIS 984

THE REFLEX INFLUENCE OF THE COLON, APPENDIX AND GALLBLADDER ON THE STOMACH. FRED M. SMITH, M.D., AND GEORGE H. MILLER, M.D., IOWA CITY 988

THE ALKALINE TIDE AS A METHOD OF STUDYING GASTRIC ACIDITY. ROGER S. HUBBARD, PH.D., CLIFTON SPRINGS, N. Y. 994

METABOLISM OF OBESITY: VIII. BASAL METABOLISM AND INSENSIBLE PERSPIRATION DURING A PERIOD OF REDUCING WEIGHT. CHI CHE WANG, PH.D.; SOLOMON STROUSE, M.D., AND MARIE ANDERSCH, B.S., CHICAGO 1002

THE ORIGIN OF UROBILINOGEN: A CLINICAL EXPERIMENT. I. M. RABINOWITCH, M.D., MONTREAL, CANADA 1014

THE CORRELATION OF WIDAL'S POSTDIGESTIVE LEUKOPENIA AS A TEST FOR LIVER FUNCTION WITH THE NORMAL RHYTHM OF THE LEUKOCYTES. MORRIS GOODMAN, M.D., AND JOSEPH E. CONNERY, M.D., NEW YORK 1018

SPHENOPALATINE PHENOMENA: PRESENT STATUS OF KNOWLEDGE. HIRAM BYRD, M.D., IN COLLABORATION WITH WALLACE BYRD, A.B., DETROIT 1026

THE INFLUENCE OF AURICULAR CONTRACTION ON THE FIRST HEART SOUND AND THE RADIAL PULSE. CHARLES C. WOLFERTH, M.D., AND ALEXANDER MARGOLIES, M.D., PHILADELPHIA 1039

SERUM TREATMENT FOR CHRONIC ULCERATIVE COLITIS. J. ARNOLD BARGEN, M.D.; EDWARD C. ROSENOW, M.D., AND GEORGE F. C. FASTING, M.D., ROCHESTER, MINN. 1063

BOOK REVIEWS 1072

GENERAL INDEX 1073